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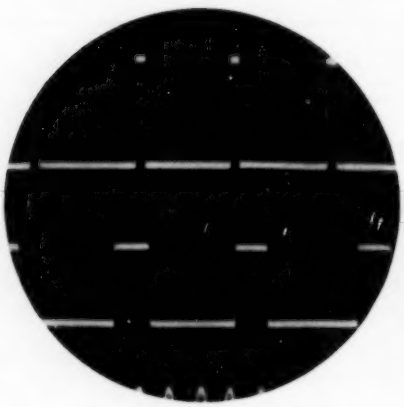

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1. Gerhard Hirschfeld and Joseph Bell *Diseases of the Nervous System* **12**: 3-7, September, 1951.
2. Gerhard Hirschfeld *Journal of Nervous and Mental Diseases* **117**: 323-328, April, 1953.
3. W. T. Liberson *Psychiatric Treatment* Vol. 31 of Proc. A.R.N.M.D. Williams and Wilkins, Baltimore, 1953.

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Archives of Neurology and Psychiatry

VOLUME 71 JUNE 1954 NUMBER 6

STUDIES ON BLOOD-BRAIN BARRIER WITH RADIOACTIVE PHOSPHORUS

IV. Spatial Aspects of Phosphate Exchange Between Plasma and Brain

LOUIS BAKAY, M.D.
BOSTON

PREVIOUS observations showed that the rate at which the central nervous system incorporates phosphate from the plasma is slow, and the total amount taken up by the brain is relatively small. There seems to be a protective mechanism which prevents the brain from exchanging unlabeled phosphate for labeled phosphate as rapidly as other organs do. This barrier is already present in the embryonic state, although it reaches its full development only after birth.[1]

In order to by-pass the barrier, radioactive phosphate was injected into the cerebrospinal fluid directly; the result was a rapid uptake of the isotope by the brain.* The pituitary gland and the tuber cinereum are not protected by the blood-brain barrier, and their exchange of phosphate with the plasma differs essentially from that of the central nervous system proper.[4] Other non-nervous elements of the brain, such as the pineal gland, choroid plexus, and area postrema, are also outside the protection of this barrier. All these findings point out the striking resemblance between the deposition of radioactive phosphate and that of acid vital dyes in the nervous system.

Apart from this similarity, however, phosphate and dyes behave very differently. The meaning of the barrier for a vital dye is that of an impermeable, inert membrane with pores small enough to prevent the passage of dyes with large-sized particles. In the case of radioactive phosphate, on the other hand, we witness a biological process of ions taking part in a normal metabolic turnover. No part of the central nervous system is inaccessible to these ions; consequently, the barrier is not an impermeable one. Nevertheless, the difference in P^{32} uptake between the "barrier-protected" parts of the brain and the "nonprotected" parts is not less formidable. In the areas controlled by the blood-brain barrier, the exchange of phosphate between the plasma and the brain is slight and protracted. In contrast, the nonprotected areas exchange phosphate more rapidly. The exchange reaches its maximum within one hour after the injection and is followed by a rapid loss of the tracer.

According to Krogh,[5] the permeability of blood vessels in the central nervous system differs fundamentally from that anywhere else in the body, and Broman [6] in the introduction to his vital-dye studies substitutes for the term blood-brain barrier the designation "selective permeability of the cerebral vessels." The theory that the site of the blood-brain barrier is the capillary wall is not unanimously accepted.

From the Department of Neurosurgery of the Massachusetts General Hospital.

This work was supported by a research grant (B 212-C) from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, United States Public Health Service.

* References 2 and 3.

Nevertheless, isotopic investigations, revealing, as they do, a marked delay in the entry into the brain of predominantly extracellular ions (Dawson[7]), do indicate that it is located at the capillary level.

Dawson[7] stated:

It seems likely that phosphate ions can enter the brain from the blood stream by two methods: directly through the capillaries in the brain substance, and via the capillaries of the choroid plexuses and the cerebrospinal fluid. With the experimental results at present available it is impossible to come to a strong decision as to the relative importance of these two routes.

The experiments described in the following pages were undertaken in order to furnish additional data concerning the rate and location of phosphate exchange between plasma and brain.

MATERIAL AND METHODS

The experiments were performed on cats. A standard dose of 1 mc. of P^{32} was given intravenously; the animals were killed by air emboli 30, 60, and 90 minutes, 5 hours, and 1, 2, 4, 9, and 21 days, respectively, after the injection. Blood samples were taken from the heart, and cerebrospinal fluid, from the cisterna magna. The brain was immediately removed and frozen. Radioautographs of cross sections of the brains were prepared on Kodak No-Screen X-ray Film. After the autographs had been developed, various areas of the brain were isolated in the still frozen specimens, and their radioactivity was determined by scalers. For comparative purposes the final data were computed in counts per minute per milligram of fresh tissue and were corrected to the same P^{32} level in the plasma. In order to determine the rate of exchange of radioactive phosphate between plasma, cerebrospinal fluid, and brain, data were computed in terms of specific activity (counts per minute per milligram of phosphate in fresh tissue) and were corrected to the same dose of tracer per standard body weight. Correction was then made for radioactive decay to the time of injection. The rate of diffusion was determined by comparing the labeled fraction of the total phosphate content in the brain with that of the diffusible phosphate in plasma and spinal fluid. The total phosphate concentration of various portions of the brain was analyzed. In the plasma and cerebrospinal fluid the determination was limited to inorganic phosphate. My main interest being the spatial aspect of phosphate exchange in the nervous system, no attempts were made to break down the data into various organic fractions. The average total phosphate concentration was found to be 32.7 mg. per 100 gm. in the cerebral cortex of the cat, 27.2 mg. per 100 gm. in the lining of the lateral ventricles, and 41.8 mg. per 100 gm. in the mesencephalon. The average inorganic phosphate content of the plasma was 7.1 mg. per 100 cc. (5.9 to 8.1 mg.) and 2.8 mg. per 100 cc. (2.6 to 3.0 mg.) in the cerebrospinal fluid.

In five cats parts of the ventricular system were obliterated by injecting paraffin into them, hours or days before the administration of the tracer. By this method, described briefly in a previous paper,[8] it was intended to cut down the circulation of ventricular fluid in certain parts of the ventricular system and thus to determine by elimination its role in the transfer of phosphate from the blood to the central nervous system.

Under ether anesthesia, a small opening was made with a sharp-pointed trocar through a small skin incision in the skull. This hole is only large enough to allow the penetration of an 18-to-19-gauge needle. The injection of paraffin should be made in the anterior horn of the lateral ventricle, for two reasons: 1. By injecting the mass in the most anterior part of the ventricular system no trapped fluid will be left behind, and the paraffin, which solidifies very shortly after the injection, will displace the ventricular fluid by expressing it along the natural channel of circulation. 2. The main pressure during the rather energetic injection of the mass builds up in the anterior horn and exerts its effect mostly on the frontal lobes. This is tolerated well and without producing any change in the vital signs or neurologic sequelae. In fact, cats injected in such a fashion behave quite normally.

The point of the injection is 3 to 4 mm. from the midline. A more lateral approach carries a higher percentage of failure by placing the mass into the brain substance instead of the ventricular system. A short, 18-to-19-gauge needle with short bevel is inserted straight downward, or slightly medial to the opening in the skull, to a depth of 15 to 18 mm. from the external sur-

face of the skull. There is usually not enough fluid in the ventricle to verify the position of the needle by withdrawing fluid. Ordinary paraffin (melting point 56 C.) is used for the injection. It is kept melted in a hot-water bath and is colored for easier identification in the brain. The temperature of the mass should be only a few degrees above the melting point to avoid damage to the ventricular wall.

The amount of paraffin injected varied with the size of the animal, but it was usually 0.5 to 0.75 cc. The mass must be injected firmly and without hesitation to avoid premature solidification in the needle or syringe. The behavior of the cat gives a fairly good indication as to how successfully the injection has been placed. The reaction is slight if filling of the ventricular system occurs, unless too much paraffin is injected. Following a successful injection there should be no change in respiration, no inequality of the pupils, no vomiting, and no back-flow of paraffin to the surface through the needle tract. The cat should wake up promptly from the narcosis. Prolonged unconsciousness and even transient weakness of a limb are signs of faulty injection.

Paraffin solidifies within a few seconds. The injected parts of the ventricular system are somewhat dilated, but no other morphological changes are produced. The choroid plexuses are being pressed to the bottom of the lateral ventricle and to the roof of the third ventricle by the mass. The lumen of the ventricles becomes obliterated, although there remains a layer of moisture between the paraffin cast and the ventricular wall.

Obliteration of the ventricles was followed in five hours to one to three days by intravenous injection of P^{32}. The cats were killed one hour to one to four days later.

RESULTS

The specific activity of the plasma characteristically shows a declining curve, with a rapid loss of the tracer during the first few hours after the injection. This initial phase is followed by a period of slow transcapillary exchange. By comparing the specific activity of the cerebrospinal fluid with that of the plasma at various intervals after the injection, it immediately becomes apparent that diffusion equilibrium is not reached between these two body fluids as far as phosphates are concerned (Fig. 1). The highest specific activity in the cerebrospinal fluid was found between one and three hours following the administration of the isotope, and even then it did not exceed 25 to 30% of the activity in the plasma. Thereafter, the specific activity of the cisternal fluid declined even further, decreasing to 10% of the plasma. This relationship in specific activity between the two fluids was remarkably stable. The level part of the concentration curve in the cerebrospinal fluid represents true values.

The data of the first hours following the intravenous injection of the tracer probably need correction, however. A large portion of phosphate enters the cerebrospinal fluid through the choroid plexus and arrives in the ventricles. Owing to its slow mixing in the cerebrospinal fluid, it takes hours before the tracer is equally distributed in the fluid of the ventricles, cisterns, subarachnoid spaces, etc. Consequently, conditions nearest to an equilibrium between plasma and cerebrospinal fluid can be observed if, within the first hours after the injection, one compares the specific activity of the plasma with that of the ventricular fluid. However, to collect enough fluid for these determinations, cerebrospinal fluid had to be removed by cisternal puncture. Thus, during the first phase of uneven mixing, samples were obtained in which the more active ventricular component was diluted with cisternal and cervical spinal fluid. Even assuming that our data are lower than the true values of the ventricular fluid in the initial part of the curve, there is no doubt that the specific activity of the plasma and that of the spinal fluid are never equal.

As far as the speed of diffusion of phosphate and its rate of exchange are concerned, there are two distinctly different portions of the cerebrum: the surface areas

and the deep white matter. The first portion includes the external surface of the brain (cortex of the cerebrum and cerebellum, outer layer of the midbrain, etc.), as well as the internal surface (lining of the entire ventricular system and the periaqueductal region). The second portion consists of the brain proper (not including those parts previously mentioned), made up mostly of white matter and some nuclear gray matter. The diffusion of phosphate into the surface areas is relatively fast. An equilibrium is reached with the cerebrospinal fluid in one to two days, and with the plasma on the fifth day, after the administration of the tracer. The specific activity of the deep portions builds up extremely slowly. A diffusion equilibrium with the cerebrospinal fluid occurs three to four days, and with the plasma seven to eight days, after the injection. These values, obtained in cats, do not differ from those collected previously in rabbits, rats, and man.

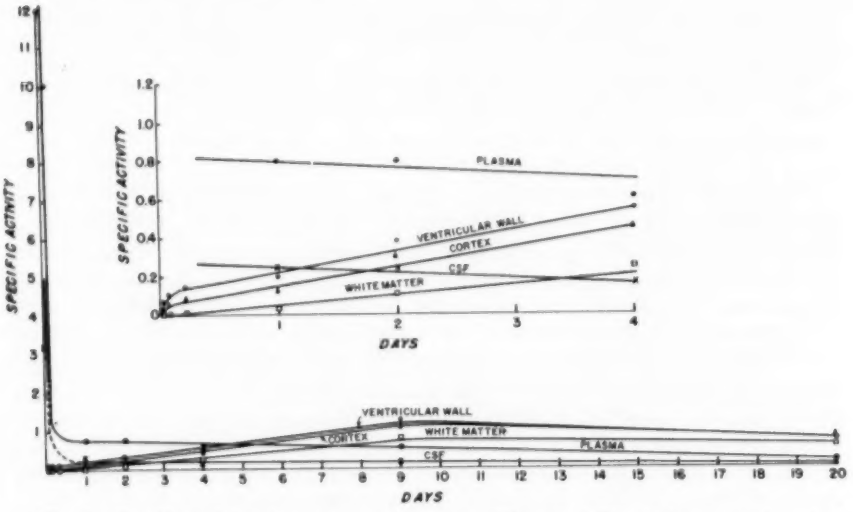

Fig. 1.—Specific activity (counts per minute per milligram of P) of plasma, cerebrospinal fluid, and brain following intravenous injection of P^{32}. Portions labeled as white matter include also gray matter of the lateral basal ganglia.

During the first hour following the injection of P^{32}, the highest specific activity is found in the ventricular lining, which shows twice as rapid an exchange of phosphate as does the cortex. At this point the deep white matter shows hardly any radioactivity at all (Fig. 1). Later the difference in various portions of the central nervous system diminishes. After the first day the specific activity of the cortex and that of the ventricular lining—histologically completely different structures, but both intimately related to the cerebrospinal fluid—become almost equal, although throughout the first week of the experiments the ventricular wall is slightly more active. The specific activity of these external and internal surfaces of the brain becomes equalized at the time of complete mixing of P^{32} in all cerebrospinal fluid compartments. The difference in phosphate exchange between the surface areas and the depth also diminishes with time (Fig. 1; Table), and their ratio changes from 10:1, on the first day, to less than 2:1, at the end of the first week; at the end of the third week the difference is even less.

A study of the phosphate exchange of the midbrain is particularly illuminating (Fig. 2; Table). This structure has practically the same diameter on cross section and is in close contact with the cerebrospinal fluid at both its inner surface (aqueduct) and its outer surface (cisterna ambiens). One-half hour after the injection of the tracer its greatest concentration is in the periaqueductal region; somewhat less is recovered from the outermost layer of the base of the midbrain and its lateral surfaces. The upper surface contains only one-half as much as the lining of the aqueduct, and the depth of the midbrain (the parts between the aqueduct and the ambient cisterns) shows only traces of radioactivity. Our present concept concerning the flow of cerebrospinal fluid corresponds with this finding. P^{32}, secreted by the choroid plexuses, mostly into the lateral and third ventricles but to a less extent also into the fourth ventricle, flows through the aqueduct into the fourth ventricle, thence to the cisterna magna and basal cisterns, and from there along the ambient cisterns

*P^{32} Content of Various Parts of the Central Nervous System**

Time elapsed from I.V. injection	30 Min.	90 Min.	1 Day	2 Days	4 Days	9 Days	21 Days
Plasma	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Cerebrospinal fluid	0.9	1.8	1.6	1.3	1.1	1.0	2.3
Cerebral cortex, mm. from surface							
1	1.1	3.2	9.6	25.0	38.0	91.0	68.0
2	0.9	1.6	7.2	19.0	32.0	79.0	62.0
3	0.4	0.8	3.2	6.7	23.0	70.0	58.0
4	0.3	0.3	0.7	5.0	18.0	57.0	56.0
5	0.2	0.3	0.7	5.0	15.0	50.0	53.0
Deep white matter	0.2	0.3	0.7	5.0	10.0-13.0	45.0-50.0	42.0-53.0
Ventricular wall							
Anterior horn	1.2	3.5	10.0	25.0	34.0	92.0	57.0
Lateral and third ventricles	2.7	5.3	12.0	32.0	40.0	80.0	59.0
Midbrain							
Around aqueduct	1.6	6.8	9.6	....	30.0	94.0	61.0
Superior surface	0.9	3.5	...	....	25.0	94.0	66.0
Inferior surface	0.9-1.3	4.0	...	....	45.0	94.0	60.0
Lateral surface	0.6-1.2	4.0	6.4	....	35.0-43.0	76.0	70.0
Depth	0.2	0.6	...	....	19.0	76.0	57.0

* Values are expressed in counts per minute per milligram of tissue and computed to a standard P^{32} plasma level.

toward the convexity. One expects to find a gradually decreasing P^{32} concentration in the neighboring structures along this pathway until the time when the isotope becomes evenly mixed in the entire cerebrospinal fluid. Ninety minutes after the injection the activity along the entire surface of the midbrain becomes equal, although it still lags behind the periaqueductal region. The difference between the deposit of P^{32} on the surfaces and that in the depth gradually disappears, and at the beginning of the second week the entire cross section of the mesencephalon reveals practically the same concentration.

The same uniform exchange did not occur in the course of these experiments through all the layers of the cerebral hemispheres. P^{32} concentration in the surfaces and in the depth showed a difference even at three weeks after administration of the tracer. Whether this difference is due to the predominance of the gray matter of the cortex as compared with the white matter of the depth or is the result of the distance between the surface and the depth remains an open question. Previous

observations indicated that gray matter, whether cortical or nuclear, shows a more rapid exchange than white matter, presumably because of its more extensive capillary population.

There are two reasons, however, for believing the transport of phosphate via the cerebrospinal fluid to be the predominant factor in the increased activity of the

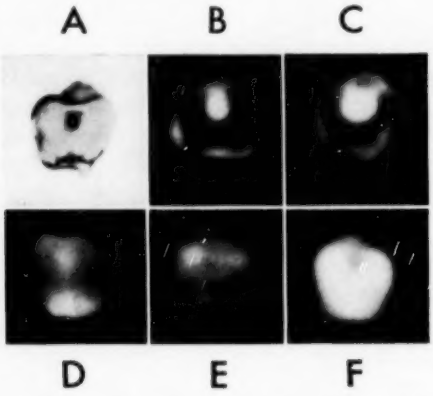

Fig. 2.—Radioautographs of cross sections of the midbrain (*A*) 30 minutes (*B*), 90 minutes (*C*), 4 days (*D*), 9 days (*E*), and 21 days (*F*) after intravenous injection of 1.0 mc. of P^{32}. Exposure time was 48 hours.

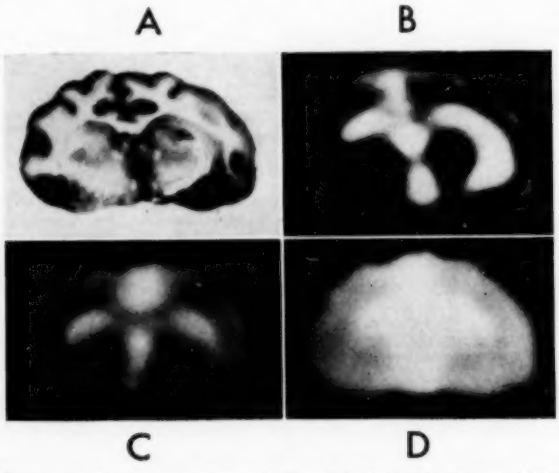

Fig. 3.—Radioautographs of cross section of the brain (*A*) 60 minutes (*B*), 9 days (*C*), and 21 days (*D*) following intravenous administration of 1.0 mc. of P^{32}. Exposure time was 48 hours.

surface areas. One is the remarkable similarity of specific activity between the cortex and the lining of the lateral ventricle, which contains mostly white matter. The other reason is based on the pattern of diffusion of P^{32} through the cortex (Fig. 3; Table). One would expect the entire cortex to show a uniformly faster phosphate

exchange than the white matter if it were caused solely by the different rates of metabolism found in these two tissues. This is not the case, however. Radioautographs and direct measurements both reveal a gradual decrease of P^{32} content as one goes from the outermost layer of the surface to the depth. In the experiments of short duration, the difference in activity between the outermost and the innermost layer of the cortex was equal to the difference between the surface of the cortex and the deepest white matter. This difference in the various layers of the cortex was present throughout the entire length of the experiments, and the most rapid exchange was limited to a 1 to 2 mm. wide strip of the surface, even on the second week after the injection.

Still another indication suggests that the bulk of P^{32} arriving at the cortex uses the cerebrospinal fluid as intermediary. A larger concentration of the isotope is

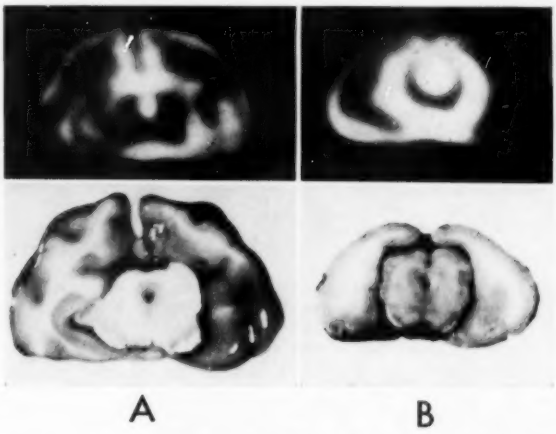

Fig. 4.—Radioautograph of transverse section of cat's brain (*A*) 30 minutes after intravenous administration of 1.0 mc. of P^{32}. Exposure time was 48 hours. Radioautograph of a corresponding section of rabbit's brain (*B*) 10 minutes after the injection of 2 μc of P^{32} directly into the cisterna magna. Exposure time was 45 hours.

found in the medial fold of the cortex, corresponding to the interhemispheric fissure, than in the rest of the convexity, which is in contact with shallower subarachnoid spaces, containing less fluid.

Examination made shortly after intravenous injection of P^{32} shows that the pattern of diffusion is identical with that in a brain injected intracisternally (Fig. 4). A much higher dose is required, however, to obtain the same concentration by the intravenous route. In this early stage of absorption, the diffusion in both cases spreads from the cerebrospinal fluid through the external and internal surfaces of the brain.

In the paraffin-injected cats various layers surrounding the obliterated ventricle were compared with similar areas on the contralateral side. One brain had to be discarded, as there was evidence of ependymal damage with local breakdown of the blood-brain barrier on the injected side. The other brains revealed virtually the same amount of P^{32} in the wall of the blocked ventricles as that found in the deep white matter, and considerably less than the amount found in either the wall of the

patent ventricles or the cortex (Fig. 5). This finding was most marked in the experiments of short duration, in which the difference between the surface areas and the depth was most pronounced. In spite of a minute amount of fluid between the paraffin cast and the wall of the ventricle, the immediately surrounding zone contained, 24 hours after the injection of the tracer, only 10% more P^{32} than the deepest white matter. At the same time this zone contained 50% less P^{32} than the wall of the patent ventricle or the surface areas. Later on the difference was less striking, partly because the difference between superficial and deep layers diminished, but also because there was some restoration of cerebrospinal fluid circulation in the blocked ventricle. Nevertheless, the effect of obliteration was still plainly visible four days after P^{32} administration. The activity in the wall of the obliterated ventricle was equal to that in the deepest portions of the brain.

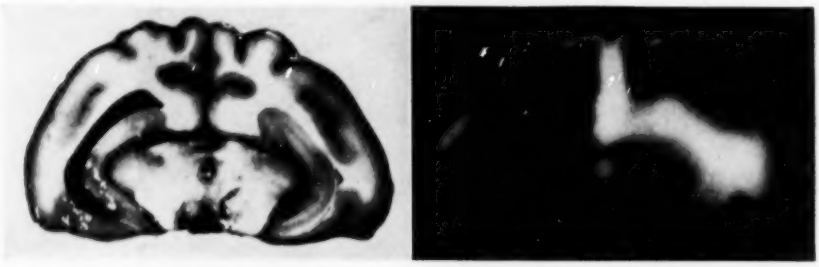

Fig. 5.—Radioautograph of cross section of a cat's brain 60 minutes after intravenous injection of 1.0 mc. of P^{32}. The left lateral ventricle was obliterated with paraffin one day prior to the administration of the isotope. Exposure time was 40 hours.

COMMENT

After intravenous injection of P^{32}, the highest concentration of the tracer can be found in the internal, as well as the external, surface of the brain, notably in the cortex and the ventricular lining. The periventricular areas reveal a particularly high activity during the first hours following the injection. The presence of the choroid plexus (containing, since it is outside the blood-brain barrier, large amounts of P^{32}) does not account for this finding. The same high concentration of P^{32} is found in the ventricular wall after the choroid plexus is removed from the specimen; also, the same amount of tracer is found in the lining of portions of the ventricular system, such as the anterior horns and the aqueduct, which do not contain choroid plexus. This phenomenon can be explained by an exchange of phosphate between the cerebrospinal fluid and the adjacent parts of the brain. Such a process was strongly suspected [2] from the concentration curves of P^{32} for the plasma, as well as for the cerebrospinal fluid, following intravenous injection.

Greenberg and associates [9] determined the ratio of the concentrations of various labeled ions in the cerebrospinal fluid to the concentrations in the plasma. In their experiments on dogs the ratio of P^{32} attained a value of 15% in the first hour and of 23% in two and one-half hours, tending to fall off after that. They obtained the spinal fluid samples by lumbar puncture. My findings in cisternal fluids are similar, however. Complete diffusion equilibrium between the phosphate of the plasma and that of the cerebrospinal fluid was never reached, and the difference between the

specific activities of the two fluids became constant after the first few hours. The ratio between the P^{32} in the cisternal fluid and that in the plasma did not reach values equivalent to those obtained by chemical analysis, even after a considerable length of time. The specific activity of the cisternal fluid was constantly lower, indicating an additional exchange of labeled ions between the cerebrospinal fluid and the central nervous system. It can be assumed, therefore, that the difference between the concentration of P^{32} leaving the blood stream and penetrating into the cerebrospinal fluid and the actual concentration found in the cisternal fluid after the mixing is complete, reveals the amount of isotopes exchanged with unlabeled phosphates of the brain. In addition, the high initial concentration of P^{32} in the periventricular layers, as compared with other areas, suggests strongly that a large portion of the plasma phosphates enters the cerebrospinal fluid through the choroid plexus. When a part of the ventricular system is filled with paraffin and the ventricular fluid cannot act as an intermediary of phosphate transport, the absorption of P^{32} is delayed in the wall of the obliterated compartment.

The fact that the P^{32} concentrations in the cortex and the ventricular wall—two very dissimilar structures—are roughly equal from the time when the tracer is equally distributed in the cerebrospinal fluid speaks strongly for a local exchange of phosphate between the brain and its surrounding fluid. The same situation exists in regions having different structures, such as the midbrain and the medulla. There are probably additional factors involved in the phosphate absorption by the external surface of the brain, especially the cerebral cortex. One of these factors might be an additional source of P^{32} arriving in the subarachnoid fluid directly through transcapillary diffusion from the meningeal vessels. Sweet and Locksley† discovered recently that another predominantly intracellular ion, potassium, normally enters the subarachnoid space directly from the blood. The other factor is the phosphate-binding capacity of the gray matter. It was found that gray matter, cortical as well as nuclear, has a faster phosphate exchange than white matter. Snyder, Abood, and Gerard,[10] using isolated layers of rat's brain, demonstrated that the white matter exhibits oxidation, glycolysis, and other metabolic rates a third lower than the cortex. It is also true that the capillary population of the cortex is about three times as abundant as that of the white matter, and this, of course, could be reflected by a larger accumulation of P^{32} in the cortical gray matter following intravenous injection. This point is undoubtedly of importance in the late phase of phosphate exchange, after a diffusion equilibrium between the fluids and various structures and layers of the brain has been reached, or at least approached; it seems to be of little importance during the initial phase of exchange. The sharp decline in specific activity of the cortex itself as the distance from the surface increases cannot be explained on the basis of transcapillary exchange.

We have no reason to believe that the tracer follows any particular pathways of absorption within the brain. The process starts with a diffuse imbibition of the superficial layers. This is true even for much larger particles (vital dyes), and there is no reason to believe that the perivascular spaces play an important role under normal hydrodynamic conditions, as was suggested by Sacks and Culbreth [11] (Spatz,[12] Schaltenbrand,[13] and Bakay [14]).

† Sweet, W. H., and Locksley, H.: Studies of Formation, Flow and Absorption of Cerebrospinal Fluid: III. Multiple Tracer Experiments in Man, read at the 19th International Physiological Congress, held at Montreal, Aug. 31 to Sept. 4, 1953.

It has already been clearly proved that there is a rapid interchange of phosphate between the cerebrospinal fluid and the brain substance (Bakay and Lindberg,[2] Sacks and Culbreth [11]). But there is no agreement on the role that the cerebrospinal fluid plays in the phosphate supply of the brain. Sacks and Culbreth arrived at the conclusion that P^{32} is made available to the brain for turnover entirely through the cerebrospinal fluid. Abood, Gerard, and Tschirgi [15] challenged these authors by pointing out the importance of phosphates in the utilization of glucose by the brain. Their opinion was that the cerebrospinal pathway is not an essential, or even important, route for the exchange of substances, such as metabolites, with the central nervous system.

It is not likely that the wall of the cerebral capillaries is entirely impermeable to phosphates. The concept of a blood-brain barrier for ions cannot mean a completely impermeable wall. Yet, it at least slows down the diffusion of phosphate ions from the plasma, while at the same time phosphate ions pass through the choroid plexus into the ventricular fluid in greater quantity, although still not as easily as into other body fluids. Once in the cerebrospinal fluid, these ions are taken up rapidly by the central nervous system. A diffusion equilibrium between the phosphate of the ventricular fluid and the subependymal zone takes place probably within a few hours after the injection; the same equilibrium involves a larger layer of the ventricular wall within one to two days.

A dualistic theory could serve as a working hypothesis to explain the diffusion of phosphates from the blood into the central nervous system. During the initial phase of absorption, P^{32} enters the brain via the cerebrospinal fluid after it has passed the blood-cerebrospinal fluid barrier. This phase is characterized by a large concentration of the tracer in the surface areas and a decline in activity of the cerebrospinal fluid. The pattern of diffusion is the same whether the tracer has been injected intravenously or intracisternally. The later phase of absorption shows slow and gradual increase of P^{32} concentration in the entire brain, presumably due to a direct passage of the tracer through the blood-brain barrier by transcapillary exchange. The process marking the initial phase remains superimposed on this later phase but loses its importance as time elapses. Hence, the difference in P^{32} content between the surface areas and the depth becomes less pronounced, although it is still slightly perceptible three weeks after the injection. This, of course, is a simplification of an extremely complex metabolic process. In addition, this dynamic equilibrium consists of a continuous chemical exchange of phosphate among various fractions and an anatomical exchange among layers of various concentration.

SUMMARY

The concentration of P^{32} and the specific activity of plasma, cerebrospinal fluid, and various parts of the brain were determined in cats over a period of 30 minutes to 3 weeks after a single intravenous injection of the isotope.

The concentration curves indicate an early exchange of phosphate between the cerebrospinal fluid and the central nervous system. Diffusion of P^{32} from the ventricular fluid into the surrounding brain tissue can be delayed by obliterating the ventricle with paraffin prior to the injection of the isotope.

The distribution of P^{32} in various parts of the brain, shortly after the injection of the tracer, is the same whether it is injected into the blood or directly into the

cerebrospinal fluid. A much higher dose is required, however, to obtain the same concentration in the central nervous system if the intravenous route is used.

Considerably higher phosphate exchange was found in the surface areas, both externally and internally, than that found in the depth of the brain. An equilibrium between these different areas was approached, but not quite reached, at the end of three weeks. The possible reasons for these differences are discussed.

Plasma phosphate enters the central nervous system by transcapillary exchange and by an indirect route, using the cerebrospinal fluid as intermediary. A theory combining these two factors is offered.

Mrs. Diana Duncan assisted in the experiments and in the analysis of specimens.

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SUITABILITY OF TUMOR-BEARING MICE FOR PREDICTING RELATIVE USEFULNESS OF ISOTOPES IN BRAIN TUMORS

Comparative Clinical and Laboratory Study in Localization and Treatment of Brain Tumors with P^{32}, Na^{24}, K^{42}, and Sodium Borate

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IN CONNECTION with investigations being pursued in this laboratory on the application of atomic energy methods to the diagnosis, localization, and treatment of brain tumors,[1] it has been necessary to screen a variety of radioactive isotopes and compounds of stable isotopes having useful nuclear properties, to determine which among them possess superior biological characteristics in regard to concentration in brain, brain tumor, and muscle.

This screening of isotopes was carried out at first mainly in selected brain tumor patients. However, the paucity of suitable patients, the wide variations in their physiological status, the variety of tumor types encountered, and the frequent compromises of experimental discipline imposed by transcendent clinical necessity rendered this method of study slow, tedious, and at times difficult to interpret. As a means of circumventing these problems, it occurred to us that most of the desired information about a given isotope might be obtained through carefully controlled studies of distribution and concentration ratios in the organs and tumors of pure-strain mice bearing transplantable subcutaneous brain tumors. Furthermore, the uniformity of the pure-strain mice and their tumors as an experimental substrate offered a possibility of a rapid method of screening without the necessity for a large statistical sampling. Although there is no assurance at the outset that data obtained in mice will carry over entirely to man, it is a relatively simple matter to check a small group of patients in order to establish a "factor of correlation" which integrates such differences as excretion, species metabolic rate, and characteristics of the particular mouse tumor studied.

To establish the validity of this principle for the study of brain tumors, we have undertaken a comparative study in mice and patients of the distribution and relative concentrations of the physiological intracellular ions $P^{32}O_4$ and K^{42}, of the extra-

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cellular ion Na^{24}, and of the nonphysiological borate ion, which is concurrently being used experimentally in the neutron-capture treatment of human brain tumors at Brookhaven National Laboratory.[2]

In this paper we wish to report the results of this study as the basis for concluding that pure-strain mice bearing transplantable gliomas provide a useful tool in studying comparative biological characteristics of isotopic compounds, and that such data can be used with reasonable confidence to predict the behavior of the isotopes or compounds in human brain and brain tumors. In a subsequent paper we shall report the results which have been obtained in applying this technique to the study of a series of positron-emitting isotopes, including Cu^{64}, Mn^{52}, Rb^{84}, and As^{74}, which further substantiate this conclusion.

EXPERIMENTAL METHODS

On the neurosurgical service of the Massachusetts General Hospital a tracer dose of some radioisotope useful in probe-counting localization, usually P^{32}, is given nearly all patients having craniotomy for suspected brain tumor.[3]

One or 2 mc. of P^{32} is given intravenously, from 1 to 24 hours before the anticipated time of probe counting. Serial biopsy sampling of tissues during the operation is necessarily subject to surgical expediency, but in this series we attempted to sample temporal muscle during the turning of the bone flap and at the time of closure, and tumor at intervals during the process of resection. "Normal brain" is obtained from the periphery of the block resection as far from obvious tumor involvement as possible. Where possible, gray matter and white matter are assayed separately, and in doubtful cases their freedom from tumor invasion is ascertained histologically. Where variation within the tumor is grossly apparent, representative samples are taken for both radioactivity assay and histological section. Venous blood samples are taken, and counts are made on both whole blood and plasma.

The amount of tissue required for counting is of the order of 100 mg. The best part of the specimen is blotted and spread thinly on an aluminum counting planchette, previously coated with a saturated alcoholic solution of lecithin and dried on a slow hot plate. The lecithin film serves later as a tissue-to-metal adhesive.[4] The wet tissue is rapidly weighed on an analytical balance and dried either on a slow hot plate or under an infrared lamp in preparation for Geiger counting. This process also establishes the adhesive bond.

The mouse brain tumors used in our experiments were induced originally by implantation of 20-methylcholanthrene, according to the method of Seligman and associates,[5] in the laboratory of Dr. Harry Zimmerman,* and they have since passed through over 50 generations of subcutaneous transplantations in mice of the same strain. Although a number of histological types of mouse brain tumors have been induced, we have used only two, classified by Zimmerman as glioblastoma and astrocytoma. The mouse glioblastoma, carried in the C-57 black strain, matures to a size of about 1 cm. in about two weeks and in another week usually ulcerates the skin and becomes necrotic and infected. The astrocytoma is carried in the C_3H strain and grows more slowly, maturing in three to four weeks and being usable for about two weeks thereafter. The tumors have usually been transplanted by trochar injection of a millimeter cube of tumor. Two to four transplants are made into each mouse in the axillae and groins so that biopsy sampling could be done from two to six times during the course of an experiment. This gives a margin of safety in allowing for necrosis in the tumor and inadvertent interference with major blood vessels to the tumor.

At first specimens of normal brain were taken via tiny bilateral parieto-occipital burr holes with a 13-gauge round-end trochar needle, directed diagonally forward into the frontal area. A 10 to 15 mg. plug of tissue was then withdrawn, a technique analogous to the use of a cork borer. This procedure did not prove fatal to the mice, even after what amounted to bilateral

* Dr. Zimmerman, Chief of Pathology, Montefiore Hospital, New York, aided in the establishment of our mouse brain tumor colony.

frontal lobectomy. With a third sample taken at the time of autopsy, this technique allowed studies over a period of hours. However, there was almost always considerable bleeding with each brain sampling, the mice were obviously made very sick, and there was fairly wide scatter in the brain data. Early in our experiments with pure-strain mice it became evident to us, as it has been to others, that the biological behavior from mouse to mouse, and from time to time in the rates of uptake of various isotopes, is remarkably uniform. This is undoubtedly a consequence of the fact that the pure strains are such highly inbred brother-sister matings for at least 20 generations that litter mates are the genetic equivalent of identical twins. Furthermore, they have lived in the same cages on the same diet all their lives and are selected for each experiment of the same age, sex, and approximate weight. On the basis of this observation, it was clear that serial autopsy of normal mice in a uniformly handled group was a technique superior, as far as organ studies were concerned, to serial biopsy in an individual mouse, and accordingly the brain-biopsy technique was abandoned.

The mouse experiments were carried out over a continuous period of 12 to 24 hours.† The mice were divided into four groups. The first group, consisting of about 10 Strong A-strain male mice of 20 to 25 gm. in weight, was used to study the uptake curves of the various organs and provided our standard "normal curves." A second group, of four to six A-strain mice, was used to provide information on the behavior and clearance rate of the blood following intravenous and intraperitoneal injection of the isotopes. The third and fourth groups were tumor-bearing mice, whose neoplasms were serially biopsied, with a time overlap among the individual mice. Organ studies were also done at the time of the last tumor biopsy to facilitate comparisons with the standard normal curves. Thus, any deviations which might result from strain differences, faulty injection of the isotope, or the repetitive procedures would be detected.

Radioactivity was measured with a standard end-window Geiger-Müller counter in a conventional lead tower. Calibrated long, half-life beta standards of the isotope under investigation, prepared in known dilution, were counted periodically along with the tissues. Doses of 1 to 2 μc (in 0.01 or 0.02 cc.) per gram mouse were used for convenience in counting and statistical accuracy. Sampling weights were kept within limits set by considerations of weighing accuracy, counting rates, and self-absorption. These were between 10 and 20 mg. for mouse blood, 30 to 40 mg. for mouse tissues and tumor, and about 80 to 100 mg. for human biopsy specimens and blood. Assuming the average dry weight to be 20 to 25% of the weight of wet tissue, self-absorption becomes a significant factor for the larger samples. With P^{32}, for example, our maximum tissue density of 20 mg. per square centimeter (when dry) introduces a counting rate loss by self-absorption of approximately 10%. The data presented below have been corrected for resolving time losses, background activity, radioactive decay, self-absorption, counting geometry, and dosage. The final results are expressed as the percentage of total injected activity per kilogram of sample weight in man (normalized to a body weight of 70 kg.). Since this unit in man is per one-seventieth body weight, we have used the analogous unit in mice.

The extracellular space in the organs and tumors of the mice we have measured as the Na^{24} space. The difficulty of obtaining sufficient plasma from a mouse to make this determination was solved by giving 1 mg. of heparin about 15 minutes before bleeding from the carotid artery. The blood was then centrifuged in a standard Wintrobe sedimentation tube, the hematocrit read, and the plasma drawn off. When only small amounts of blood were available, it was centrifuged in a micro-Hinton tube or a capillary tube, and the plasma and packed cells were separated by breaking the glass tube at the appropriate point. K^{42} distribution was similarly measured.

Since there is no usable radioisotope of boron, our sodium borate U. S. P. (Borax) data were obtained by chemical analysis, employing the method of Ellis, Zook, and Baudisch.[6] This consists of oxidative-acid digestion, coupled with the dye, 1,1'dianthrimide, and spectrophotometric comparison with standard solutions. The sampling of tissues was gauged to a total boron content in each sample of between 1 and 10 γ. The samples, ranging from 30 mg., for blood, to 150 mg., for brain, were weighed on wax-coated celluloid squares and then quick-frozen. In this solid

† Assistance was given by the Misses Janette Robinson and Barbara Chick and Mrs. Irene Gatto Didtschenko, of this laboratory, and by Jason Starr and John Cadigan, of Harvard Medical School.

state quantitative transfer to boron-free reaction tubes was readily effected.‡ The human boron data presented here for comparison are from Sweet and Javid [7] and have been replotted from their original data, based on their standard dosage of 8 mg. of boron, as sodium borate per kilogram of body weight. In the mouse experiments, since we were obliged to use smaller sample weights, the dose was increased to five times that of the human dose, or 40 γ of boron per gram of mouse.

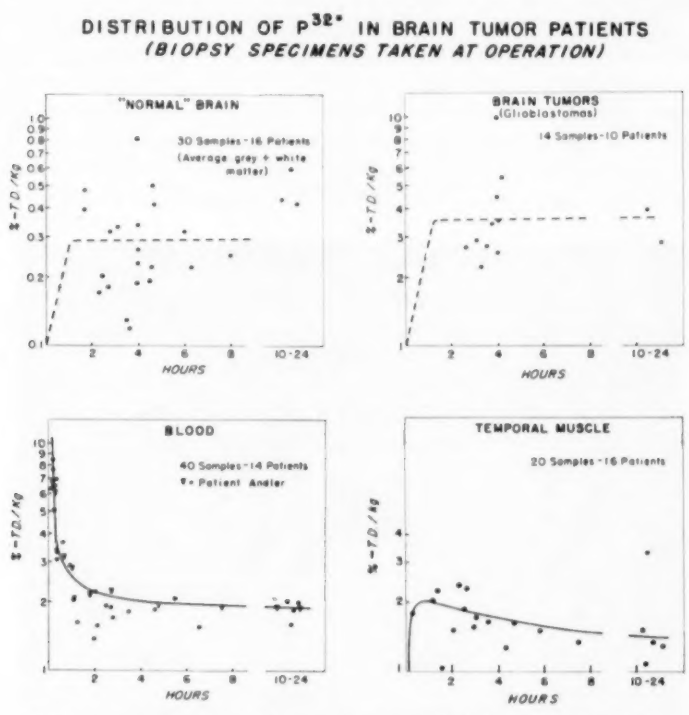

Fig. 1.—In these graphs the number of points plotted is less than the number of samples, owing to the results being averaged from closely spaced samples in the same patient. The blood curve was drawn through the points obtained from one patient only.

RESULTS AND COMMENT

P^{32}.—By virtue of its intimate association with metabolic processes and ideal nuclear properties as a tracer isotope, P^{32} has been a favorite ion for study. In the realm of brain surgery its usefulness in the localization of deep tumors is already of practical importance.[3] It seemed, therefore, a logical criterion to use in establishing the relative behavior of human and mouse brain tumors.

In order to minimize the wide scatter of data which are inherent in studies of this sort on patients at operation and to achieve a more reliable comparison, we

‡ This technique for weighing and quantitative transfer was devised by Mrs. Irene Gatto Didtschenko. In the frozen state the hardened wax separates from the celluloid, rather than the tissue from the wax. The wax which goes over with the sample does no harm, since it is free of boron.

selected a small group of patients for study and employed the same rigid controls in laboratory technique established for our mouse experiments, rather than use the much larger amount of routine P^{32} counting data from the clinic obtained under variable circumstances by many workers. Figure 1 presents these data obtained from 16 patients with glioblastomas on whom biopsy was done at operation, each patient contributing a span of from one to three hours to the composite picture. It will be noted, as in Figure 6, for boron, that even in this selected group there is considerably wider scatter than in the mouse data for the same isotopes. A number of factors undoubtedly contributed to this: the variations in disease status among the patients; the degree of clinical shock at the time of operation; alterations in the blood and intracellular fluid compartments attendant on hemorrhage; transfusion and intravenous infusion during operation; the variability of tumor characteristics, such as vascularity, growth rate, and cellular compactness, even among those of the

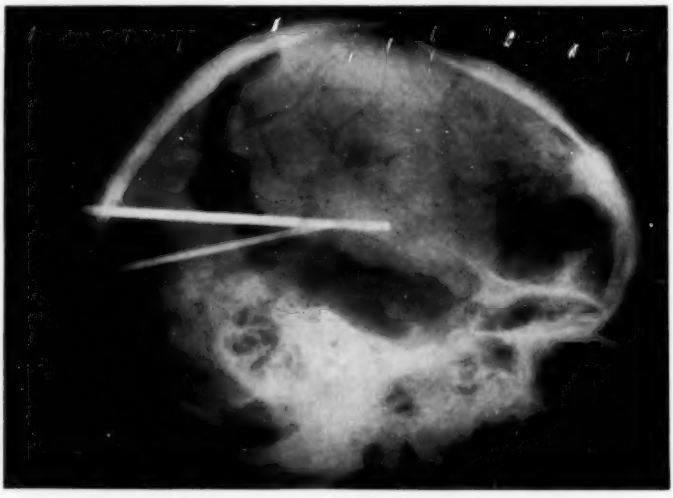

Fig. 2.—Cranial roentgenogram showing Geiger-Müller probe counters in position.

same histological type, and, finally, the difficulties of assuring uniform sampling during the rigors of intracranial operations. Surprisingly, the most striking scatter is seen in the case of brain whose metabolic activity and exchanges with the blood are presumed to be closely guarded by the blood-brain barrier. Apparently, considerable alteration in the permeability of the barrier can occur as a direct result of surgery, from administration of 50% sucrose to counteract cerebral edema, or subsequent to diagnostic ventriculography or iodopyracet (Diodrast) angiography, which is frequently carried out a few hours before craniotomy.

In contrast to these unavoidable liabilities in studies on brain tumor patients, the consistency of the data obtained from mice from one experiment to another points graphically to a remarkable constancy of their blood-brain barrier and to the admirable experimental substrate they provide.

The scatter in the all-important brain and tumor data of Figure 1 precluded drawing any convincing uptake curves. The need clearly existed for a means of

obtaining continuous and coherent uptake data over a period of several hours in an individual patient so that the shape of the curve could be clearly established. To this end we developed a technique for continuous intracerebral probe Geiger counting.*§

Figure 3 presents data obtained with P^{32} in a typical case of continuous Geiger probe counting. Counting was carried out continuously for 6 hours and intermittently thereafter up to 96 hours. When these data are compared with those obtained by pan counting of biopsy specimens shown in Figure 1, it is seen that their correspondence is well within the limits of experimental error and individual variation. The difference in activity level at which the brain appears to reach a plateau in the two cases demonstrates the value of probe counting in elucidating the shape of the uptake curve. In both cases the brain activity rises abruptly after injection to about 0.3 unit. The scatter in the composite data from pan counting is too great, however, to allow any commitment as to the shape of the curve thereafter, and, accordingly,

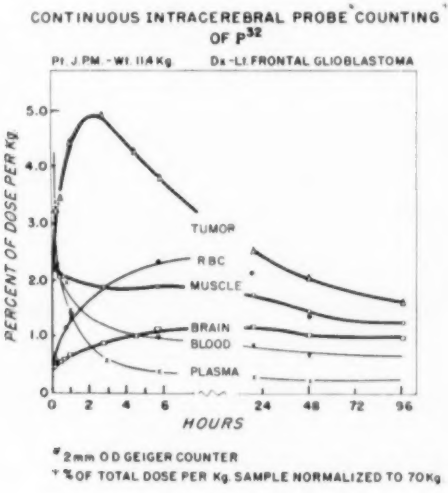

Figure 3.

a horizontal dotted line is used to indicate an average value. Continuous probe counting, on the other hand, clearly demonstrates a slow, steady rise in activity after the

§ This technique is essentially an extension of the practice of probe-counting localization of deep tumors at the time of craniotomy. With suitable fixation of the probes (their size is about that of a ventricular needle), it is possible to count continuously or intermittently in the same area for several hours, during which time the patient lies in bed in reasonable comfort except for limitation of movement. We have employed this technique only in patients with large malignant tumors which are not amenable to complete removal. Figure 2 is the skull x-ray of such a patient demonstrating the position of the probes during counting. In one of the probes the 1-cm. sensitive volume may be seen near the tip with the anode wire traversing it. Since the probe is primarily sensitive to beta particles, the count obtained represents the activity of a small volume of tissue surrounding the probe, activity from beyond being largely absorbed in passage through the tissue. In the case of P^{32}, 99% of the activity recorded originates within a radius of 5 mm. from the probe. For K^{42}, which emits a very high-energy beta particle, the 99% radius is 12 mm. The data have been converted to per cent of injected dose per kilogram of tissue by dip-calibrating the probes in standard solutions of known activity.

initial abrupt phase, which continues for 6, and possibly as long as 24, hours. Likewise, the curve for uptake in tumor shows a prominent peak at two hours, so that the highest tumor-brain ratios in the malignant gliomas are attained at less than two hours following injection of the isotope.

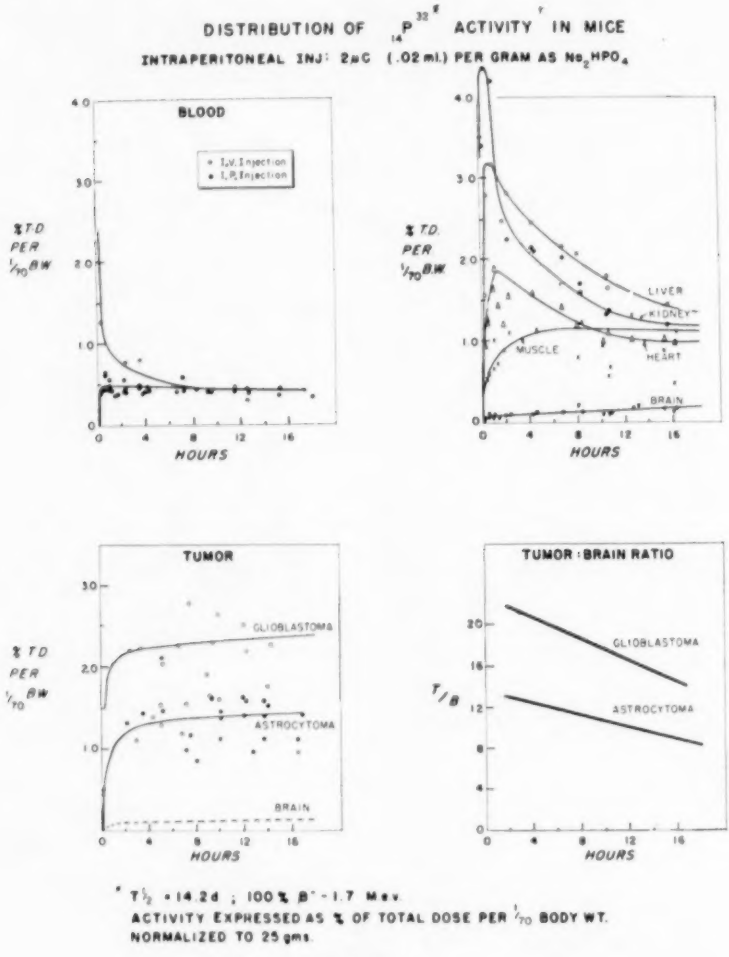

Figure 4.

The distribution of P^{32} activity in mice after intraperitoneal injection is shown in Figure 4. The curve for liver may be taken as representative of spleen and adrenal glands as well, since these organs showed almost identical curves after two hours. They differ, however, in the rate of initial rise and in their peak values, which are reached in about one hour. Kidney shows the most rapid rise and fall, and reaches the highest activity attained by any tissue, indicating that kidney has the highest

turnover rate of phosphate among the organs studied. The statement of Pitts and Alexander [9] that PO_4 is actively reabsorbed in the tubular epithelium gives credence to this supposition.

It may be noted that the mouse tumors show a greater amount of scatter than the mouse organs, although less than human tumors. Since there is fairly uniform progression in uptake in successive tumor biopsy specimens in the same mouse, the variability from mouse to mouse suggests differences in the blood supplies which the tumor transplants have been able to marshal.

Comparing the data obtained for mice with those obtained for patients, we see that the behavior is qualitatively the same: In all organs except brain there is a rapid rise in activity, the peak being reached within a few hours. Brain activity, on

TABLE 1.—*Comparison of P^{32} Ratios in Patients and Mice Four Hours After Injection* *

	Patients	Mice
Tumor-brain ‡	10-20	10-20
Tumor-muscle	2	1.4
Muscle-brain	7	10
Blood-brain	6	4
Muscle-blood	1-1.5	2.4

* Intravenous in man; intraperitoneal in mice.
‡ All tumors were glioblastoma.

TABLE 2.—*Extracellular Space (E. C. S.) in Mice Measured with Na^{24}* *

Mouse Space	Time, Hr.	Brain	Heart	Muscle	Liver	Spleen	Pancreas	Kidney	Adrenal
1	4	30.7	24	13.9	21.5	20.2	16.1	39.4	27.9
2	5	29.1	30.4	11.8	20.5	18.9	22.0	35.3	27.6
3	6	28.2	24.3	11.1	18.5	19.0	21.0	30.5	21.9
6	9	29.4	22.5	13.9	....	17.9	16.6	41.5	26.1
4	10	31.3	22.4	12.3	17.8	19.3	20.6	41.2	28.1
8, 10	27	27.9	23.5	15.9	....	....	....	....	....
Mean:		29.7	23.3	12.6	19.6	19.0	19.3	37.6	26.3
Average deviation:		± 1.0	± 1.9	± 1.0	± 1.3	± 0.6	± 2.3	± 3.7	± 1.8
E.C.S. Na^{24}, % of tissue weight:		30	23	13	20	19	20	38	26

* Intraperitoneal injection, 2 μc (0.01 cc.) per gram.

the other hand, rises much more slowly, has a lower absolute level, and does not reach equilibrium for many hours, in mice apparently still rising after 16 hours. There is also a striking quantitative comparability in the two species. All the tissues studied except brain and blood approach an equilibrium between 1 and 2 (per cent per one-seventieth body weight). The somewhat lower P^{32} level in mouse blood suggests a lower phosphate content in mouse erythrocytes.

In Table 1, a summary of the comparative behavior of P^{32} in man and mouse is presented in terms of the activity ratios observed among various tissues.

Na^{24}, Extracellular Space Measurements.—In the early period after intravascular injection of an isotope, one of the important factors determining differential concentration in the various organs is their relative extracellular volumes. We have therefore studied the isotope distribution of the major extracellular cation, Na^{24}, as a measure of the extracellular spaces of the various mouse organs. These data are presented in Table 2. The similarity of the values for all tissues from 4 to 27 hours

indicates that equilibrium was reached in the extracellular fluid sometime before 4 hours, even for brain. Each tissue has its characteristic extracellular space (E.C.S.): muscle, the lowest, at 13%; heart, liver, spleen, and pancreas, close to 20%, and brain and kidney, high values of 30% and 38%, respectively. The most cogent comparison with these data would be, of course, similar data for human organs. Such a study, however, is both socially and technically difficult, since it involves pre-

TABLE 3.—*Comparison of Tissue Extracellular Spaces* Measured with Na^{24} in Laboratory Animals*

Animal	Brain	Heart	Muscle	Liver	Spleen	Pancreas	Kidney	Adrenal	Author
Mouse	30	23	13	20	19	20	38	26	See Table 2
Rat	31	35	15	18	..	..	38	..	Manery and Hastings [11]
Rabbit	38	36	15	21	27	..	50	..	
Dog	39 †	27 †	17	24 †	49 †	..	36	..	Harrison, Darrow, and Yannet [14]
Monkey	..	..	16	..	..	..	38	..	

* E.C.S. expressed as per cent of wet tissue weight.
† From Stern, Cole, Bass, and Overman.[15]

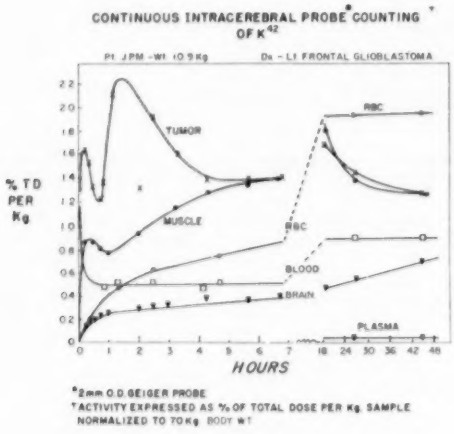

Figure 5.

mortem planning and preparation for a postmortem study and suffers further from the grossly disturbed physiological status of the moribund patients, who would be the most likely candidates. Up to the time of writing neither Na^{24} nor K^{42} studies of this kind in man have been reported in the literature. As an alternative, we have collected in Table 3, for comparison, extracellular spaces Na^{24} measurements made by other investigators in the rat, rabbit, dog, and monkey. With isolated exceptions (e. g., the very high Na^{24} space of the rabbit kidney) the extracellular spaces of the various organs show close similarity among these mammalian species. This lends another factor of confidence to the use of mice as indicators of the sort of isotopic distribution to be anticipated in man.

K^{42}: the Intracellular Milieu.—Since the concentration gradient of potassium between intracellular fluid and plasma reflects factors of both plasma-membrane permeablity and cellular metabolism, we have studied K^{42} as a third point for comparison. Figure 5 shows the curves of uptake for brain, brain tumor (glioblastoma),

and muscle in man, obtained by probe counting in a fashion similar to that described for P^{32}. The data for whole blood, erythrocytes, and plasma were obtained in the same patient by pan counting. It may be observed that the potassium in brain exchanges very slowly; equilibrium has not been reached even after 42 hours, and, as is well known, practically all the K^{42} activity in whole blood belongs to the erythrocytes. The initial spikes seen on the tumor and muscle curves are undoubtedly

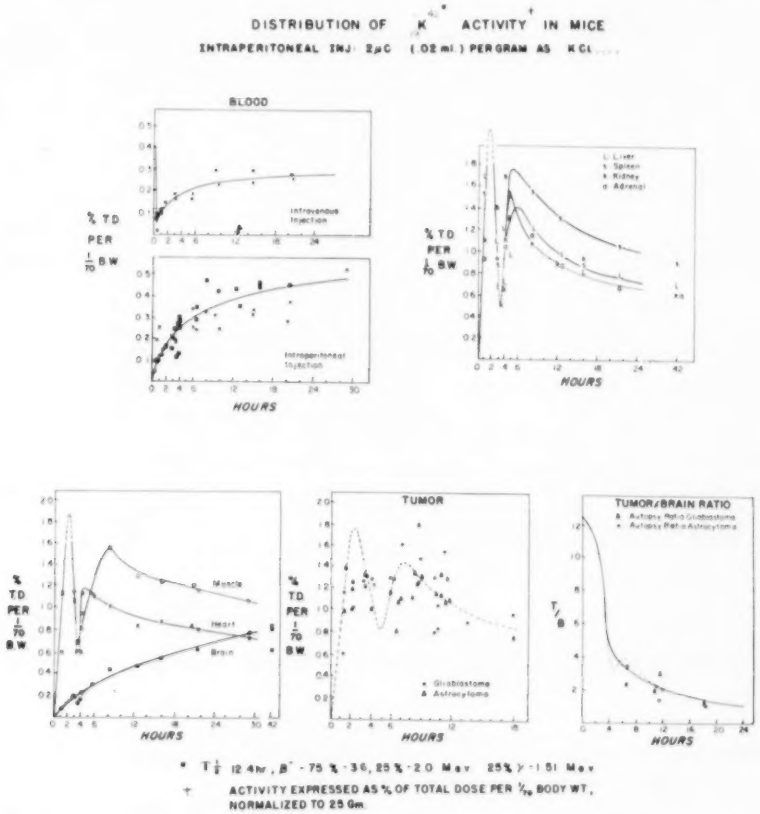

Fig. 6.—We have no explanation for the sharp secondary trough and rise occurring between three and six hours in the above normal organs except brain. The dotted portions of the organ curves represent uncertainties arising from too few points in zones of rapid change. The tumor curve is dotted because of our impression from individual mice that tumor behaves similarly. This is not clear above when all the tumor data are plotted together.

due to the K^{42} content of the extracellular fluid, which, for a brief time after injection, is higher than the intracellular K^{42}. The tumor-to-brain ratio appears to have two early peak values within the first 90 minutes, each of about 10. It then gradually declines to 4 by 6 hours and to 2.5 by 24 hours. The uptake of K^{42} by thigh muscle is somewhat slower than that of tumor, but it has caught up with the latter by about six hours, after which they remain together.

Figure 6 illustrates the behavior of K^{42} in various mouse organs and brain tumor. Heart, muscle, and the parenchymatous organs have all reached their peak in about two hours, whereas the blood (erythrocytes) and brain lag far behind. In the blood curve for intravenous injection the plasma clearance of potassium was so rapid that

TABLE 4.—*Comparison of K^{42} Activity* and Tissue Ratios Six Hours After Injection*

	Man	Mouse
Brain	0.36	0.36
Tumor	1.45	1.29
Muscle	1.36	1.61
Blood	0.52	0.74
Heart	....	1.1
Liver	....	1.3
Kidney	....	1.2
Tissue ratios		
Tumor-brain	4.0	3.6
Muscle-brain	3.8	4.5
Blood-brain	1.45	2.1

* Activity expressed as per cent of total dose per kilogram of tissue in man and per one-seventieth body weight in mice.

TABLE 5.—*Tissue-Plasma Ratio of K^{42} Activity* in Mice*

Mouse Space	Time, Hr.	Brain	Heart	Muscle	Liver	Spleen	Pancreas	Kidney	Adrenal
11	3	3.06	17.4	18.8	19.8	23.4	27.1	15.3	16.7
12	3.5	3.92	19.2	22.3	23.6	29.4	....	....	17.7
13	4	3.61	13.8	18.4	17.3	....	26.7	....	15.8
17	29	13.30	12.1	17.5	....	....	....	....	....
20	42	21.30	16.0	22.1	18.8	23.8	23.6	16.9	17.1
21	42	21.20	17.6	22.0	20.0	24.7	24.4	17.1	16.5
Assumed equilibrium ratio (42-hr. average)	21		17	22	19	24	24	17	17
Equilibrium activity ratio per gm. tissue water ‡:	25		20	27	25	29	..	20	..

* 2 μc K^{42} (0.01 cc.) per gram mouse injected intraperitoneally (tissue activity was measured as per cent of total dose per gram of tissue wet weight).

‡ Calculated on the basis of data published by Manery and Hasting,[11] for the per cent of water per gram of tissue wet weight in the rat.

TABLE 6.—*Tissue Potassium (mEq./Kg.) in Man and Laboratory Animals*

	Plasma	Brain	Heart	Muscle	Liver	Spleen	Kidney	Authors
Man	5	92.5	..	....	..	..	..	Gerrgierskova and others [12]
Mouse	4.6	87	72	101	87	99	68	Table 5
Rat	4.6	102	84	113	92	113	71	Manery and Hastings [11]
Rabbit	...	..	..	115	..	..	..	
Rabbit	...	72	54	102	66	..	60	Corsa and others [16]
Rabbit	...	..	..	79	50	53 *	..	Harrison, Darrow, and Yannet [14]
Monkey	...	..	..	....	..	76 *	..	
Dog	...	..	..	....	..	56 *	..	
Dog	...	95	81	102	74	61	..	Stern and others [15]

* Average of combined viscera.

when the first blood sample was taken, at about 10 minutes after injection, the level had fallen to less than 1% of the estimated initial value. The steep decline is therefore not evident. After these early few minutes, the intravenous and intraperitoneal curves parallel each other. The tumor-brain ratio curve has been drawn from the

smoothed curves in Figure 6, and the actual experimental ratios obtained in individual mice at autopsy have been superimposed. This ratio curve follows very closely the pattern described in man above, starting at about 12, falling steeply to 3.6 by 6 hours, and then more slowly, down to 1.8 at 20 hours. A comparison of the K^{42} activities and important tissue ratios in man and mouse is tabulated in Table 4.

In another K^{42} study we determined the activity ratio of various mouse organs to plasma at intervals from 3 to 42 hours. These data are presented in Table 5. The

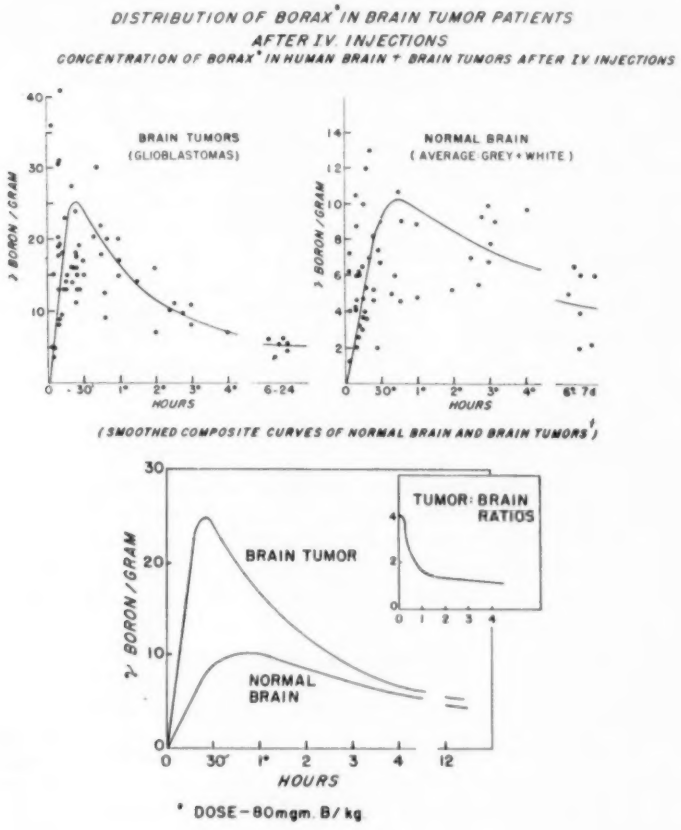

Figure 7.

potassium ratios have been calculated from the average 42-hour data, by which time we assume equilibrium has been reached, and are expressed as the ratio per gram of wet tissue and per gram of tissue water. This latter conversion was calculated on the basis of data presented by Manery and Hastings [11] for the water content of rat tissues. Multiplying these equilibrium ratios (per gram of wet tissue) by the chemical concentration of potassium in mouse plasma (taken to be 4.6 mEq./L.), we obtain the concentration of potassium in other organs. These values are given in Table 6 and compared with data reported by others for a variety of species. It may

be seen that the agreement among the species is not as close as for the extracellular sodium space. A part of the discrepancies undoubtedly represents species variation, but some must be a reflection of differences in technique, since there are significant variations in the data obtained in the same species by different investigators. The mouse data, however, are in good agreement with those of Manery and Hastings ‖ on the rat, with those of Stern and Cole on the dog, and with the isolated datum on the human brain from the U. S. S. R.[12]

Boron.—In the foregoing our efforts to validate the thesis of a comparability between mouse and man as to isotope distribution have demonstrated the following points: In the case of P^{32}, which we have thought of as an indicator of metabolic activity and biochemical energetics, gratifying similarity of behavior has been demon-

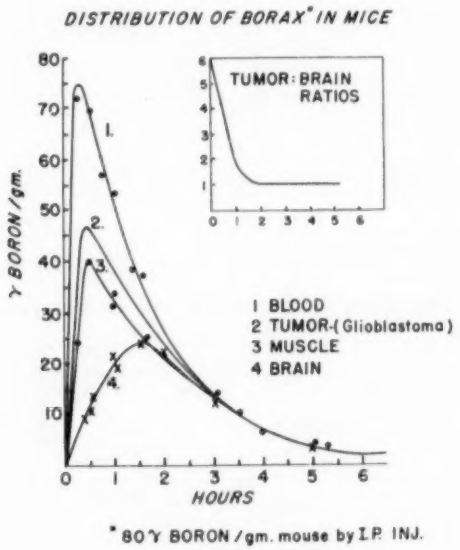

Figure 8.

strated. Extracellular space studies with Na^{24} have demonstrated good agreement among a number of mammalian species, which, in the absence of comparable human data, we have taken by extension to constitute supportive evidence for our thesis. Finally, using K^{42} as an indicator of the internal milieu and its turnover rate as an index of tissue exchange, we have again found mice to be reasonably good representatives of humans. In the following section on boron a nonphysiological ion has been used in mildly toxic concentration. Since in this case there would seem to be little a priori basis for predicting a similarity of behavior in the two groups, we felt a study of boron would constitute a rigorous test of our thesis.

‖ The data of Manery and Hastings are expressed as milliequivalents per kilogram of blood-free, fat-free tissue. Our mouse data are for carefully selected, blotted, and grossly fat-free tissue, but they have not been corrected for the estimated blood, connective tissue, and neutral lipid content. This correction could account for the 10% or so difference between these sets of data.

Figure 7 is a replot of data for boron in human brain and brain tumors (glioblastomas) previously reported by Sweet and Javid,[7] with the smoothed curves obtained. It may be observed that the ratio falls sharply from about 4 (the limiting ratio of the slopes) to slightly higher than 1 in about one hour. In mice (Fig. 8) the various tissues form a family of similar curves, such that the slower the rise time the lower is the peak and the later is its occurrence. Boron uptake by liver, spleen, and kidney also falls within this family of curves, but the values are all higher than for tumor and muscle and the rise times are faster.

As with P^{32} the ratio curve here bears a remarkably close agreement with the human curve. It was pointed out in the section on methods that the mouse dose was five times as great as the human dose calculated per gram of body weight. It is of interest to note that the boron content of the organs in the mice did not keep pace with the increment in dosage, being only two to two and one-half times the value seen in man. We have investigated the effects of dosage on tissue levels,[13] for if this observation were fully borne out, it would be of considerable practical importance in the technique of boron-neutron treatment of brain tumors now being carried out under the direction of Drs. Lee Farr and William H. Sweet at the Brookhaven National Laboratory Nuclear Reactor Department and Hospital. The calculations of effective tumor dose of alpha particle radiation, following neutron capture by boron in the tumor tissue, have been predicated on a linear proportionality between tissue level and the size of administered dose (the human treatment dose is four times that given in the uptake ratio test at the time of operation).¶

CONCLUSIONS

1. Screening isotopes directly in man has proved to be a slow and tedious method, often hard to interpret, owing to the wide scatter in data which takes place. This variability is largely a result of alterations in the physiology due to the brain operation (at which time only is sampling possible); therefore it is not relevant to, nor is it a fair representation of, the behavior to be expected of the patients when the nonsurgical diagnostic and therapeutic procedures involving nuclear energy are to be applied. The scatter observed is attributable not only to variations in tumor characteristics from patient to patient but also to the shock and extracellular fluid changes resulting from hemorrhage and infusions at the time of operation. Further, it is due to alterations in the permeability of the blood-brain barrier which occur as a consequence of diagnostic procedures just prior to operation and to the operative trauma itself.

2. By contrast, isotope studies in pure-strain mice bearing transplantable subcutaneous brain tumors have been shown to provide coherent comparative data which can be obtained rapidly and consistently. The uniformity of the mice as an experimental substrate reflects their genetic similarity, careful selection as to weight, age, and sex, uniform handling, and the fact that their tumors are all daughters of the same orginal cell type.

3. Comparative studies in mice and patients with P^{32}, K^{42}, and sodium borate (borax) have demonstrated a remarkably close agreement in the concentration ratios observed between tumor and brain. Measurements of the extracellular sodium space for the various organs in mice also show close agreement with values for rats, dogs,

¶ References 2 and 10.

rabbits, and monkeys. Studies on the potassium contents of mouse organs indicate that these fall within the range for other commonly employed experimental animals. This favorable comparison of data in mice and patients is further substantiated in our study of a series of positron-emitting isotopes, including Mn^{52}, Rb^{84}, and As^{74}. When a selection is to be made among a group of particularly favorable isotopes, however, it is desirable to obtain enough human data to define a "factor of correlation" which embodies differences in excretion, general metabolic rate, and the characteristics of the particular mouse tumor being used.

4. The most rapid and valid method we have found for obtaining these correlation data in patients is an extension of the Geiger probe technique of tumor localization, whereby continuous uptake curves may be obtained over a period of hours or days in individual patients.

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SPIKE-DOME COMPLEX IN THE HUMAN ELECTROENCEPHALOGRAM

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BETHESDA, MD.

THE SPIKE-DOME complex is a primary electric correlate of the clinical convulsive disorders. Because of its clinical importance, its striking contour, and its remarkable paroxysmal quality, the spike-dome discharge has been extensively studied in man * and, as far as is applicable, in experimental animals.[1] This communication treats of the physical characteristics and the time relations of these complexes as derived from the intact scalp of man. Many complexes were recorded by relatively high-speed photography of cathode ray traces, obtained through conventional (A.C.) amplification in order to obtain sufficient resolution of the complexes to allow time measurements within 2 msec. Other complexes were recorded by low-speed direct-writing oscillographs with direct-coupled (D.C.) amplifiers.

METHOD

Recordings were taken from more than 100 patients with various types of clinical epilepsy for the purposes of this investigation; these subjects ranged from 4½ to 29 years of age. The sex distribution was predominantly female. In all A. C., and in some D. C., recordings the electrodes consisted of solder disks with a bentonite-Cambridge conducting paste. The electrodes were fixed to the head with collodion. For some of the D. C. recordings calomel (mild mercurous chloride U. S. P.) electrodes were also used. The calomel electrodes were modifications of those described by Bishop and his associates.† From the intact scalp it was observed that the D. C. tracings derived through the two types of electrodes were identical in all measured characteristics; consequently, in the excerpts of the D. C. recordings the electrode type is not usually designated. For the A. C. records, Grass (Fig. 1) and Offner (all other Figures) amplifiers were used; the direct-current recordings were made with the Offner Type 142 D. C. amplifier operating into the Offner dynograph.

All cathode ray pictures were obtained from Electronic Tube Corporation multiple gun oscilloscopes. The A. C. amplifiers, except those used for Figure 1, were operated essentially flat between ½ and 10,000 cps. For Figure 1 the amplifiers were flat between 2 and 2,300 cps.

The majority of the cathode ray oscillograph tracings were recorded on continuous moving film, at the rate of 25 to 50 cm. per second (Fairchild-DuMont Camera Type 314). These speeds gave resolutions of 8 to 20 times that ordinarily used in clinical recordings.

RESULTS

The spike component of the full complex ranged between 40 and 70 msec. in duration; the slow-wave component ranged between 250 and 290 msec. Individual spikes, although maintaining a general similarity in contour, showed, when they were

From the United States Naval Hospital, National Naval Medical Center.

* Cohn, R.: Analysis of the Spike-and-Dome Complex by Means of High Speed Photography, American Electroencephalographic Society, 2d Annual Meeting, June 12, 1948, Atlantic City, N. J.; Panel Discussion: Petit-Mal and the Spike-Wave EEG, American Electroencephalographic Society, 5th Annual Meeting, June 17, 1951, Atlantic City, N. J.

† Bishop, G. H.: Personal communication to the author.

resolved, variable forms in successive complexes in a series. In Figure 1 it is observed that the right frontal spikes varied from flat-topped to rounded peaks of different amplitudes; a similar variation was recognized in the left frontal spikes. The double-peaked character of the occipital spikes tended to be more fixed in contour, but they, too, showed definite variations in form. Despite the demonstrable differences, the basic form of each spike was fairly well recognized in any given sequence of spike-dome complexes.

It is also observed in Figure 1 and the succeeding oscilloscope records that there was an incontestable asynchronization of the spike components of the spike-dome complexes when recorded simultaneously from homologous and heterologous regions of the head. In this Figure it is clear that the major negative deflection from the occipital pair of electrodes ordinarily preceded the spikes of the homologous frontal pairs. However, as in Line 1 in the second ensemble of complexes, any spike may

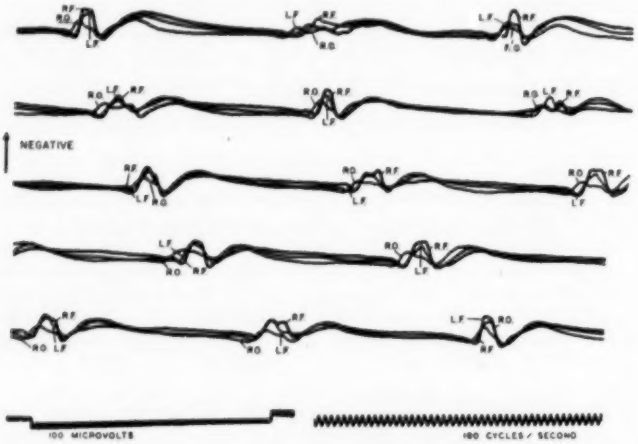

Fig. 1.—Spike-dome complexes, continuous recordings from left to right. The remarkable general asynchrony of spikes is shown. The almost precise repetitiveness of the discharges may be seen by erecting diagonals through the peaks in the successive lines. Note the extreme resolution of these complexes, approximately 15 times that ordinarily employed in ink tracings.

at times lead the other spikes by as much as 15 msec., as measured from the first negative inflection (upward in all oscilloscope records). That the first negative inflection was the proper transition segment to measure was evident from D. C. recordings, where the base line shift almost invariably became negative following the first spike. This phenomenon indicates that the spike is the "true" initial component of the complex. When the first negative inflections of the spikes were consistently measured in simultaneous tracings, it was seen that asynchronization of as much as 20 msec. was repeatedly present in the spikes originating from various parts of the brain. The low-amplitude positive deflections (first downward movement) of the discharges were sometimes synchronous with the negative wave from a homologous derivation, but this phenomenon was inconstant and consequently could not be used as indisputable evidence for invasion of the afferent signal into the homologous brain region.

The resolved slow components of the complexes were remarkably similar in contour, and in time relations, from all disparate scalp derivations. In general, there was only a moderately sharp-fronted negative deflection, which reached a maximum and then descended in a sloping plateau that was truncated, prior to reaching the base line, by the arriving spike discharges. The over-all contour thus was that of a rectangular wave, distorted by a slowly overshooting rising phase. These major features are shown in more detail in the color tracings of Figure 2. In this Figure it is observed that the left frontal spike discharge led the right frontal and occipital

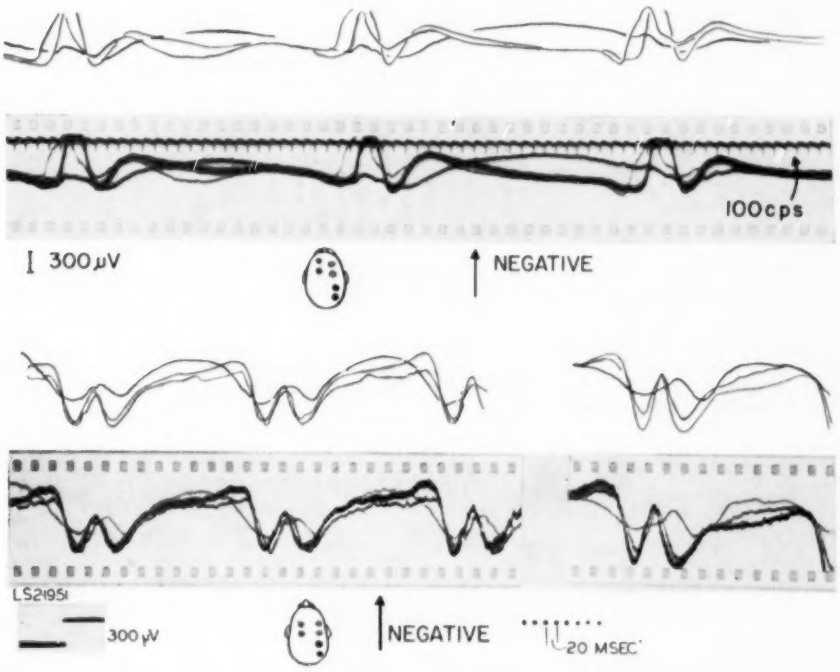

Fig. 2 (Upper).—Resolved spike-dome complexes. Color tracings are utilized to facilitate observation. Blue is left frontal; red is right frontal, and black is right occipital derivation.

Marked frontal asynchrony is recognized, with transient synchronization of the right frontal and the right occipital spikes. The roughly rectangular character of the slow components is clearly represented.

Fig. 3 (Lower).—Resolved spike-dome complexes. The asynchrony of the frontal spikes ranged about 10 msec. The right occipital spike lags by approximately 15 msec. Although the rectangular character of the slow component of the complex is apparent, its maximum negativity occurs just prior to the arrival of the spike.

spikes by approximately 15 msec.; occasionally the right frontal and right occipital spikes, despite differences in amplitude, appeared almost synchronous.

In Figure 3 the frontal asynchrony measured approximately 10 msec., with the right nearly always leading. The occipital spike lagged behind the frontal spikes by nearly 15 msec. This Figure also shows the not uncommon contours where the slow

components of the complexes, although persisting in the general rectangular wave character, had their maximum negative value just prior to the onset of the relatively positive phase preceding the spike.

Occasionally in a single patient, in a given recording, it was thought that patterning could be recognized. However, in measuring several thousand complexes from a large number of subjects, no consistent pattern of synchrony (or asynchrony) could be established.

The frontal spike asynchrony, demonstrated directly in the foregoing material, may be observed indirectly in the ordinary ink-writing oscillographs by means of effectively differential derivations through transverse leads. The results of this

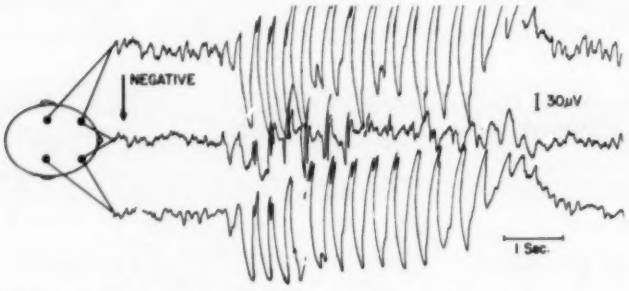

Fig. 4.—Indirect method for determining asynchrony of frontal spikes. A. C. recordings. The transverse frontal derivation, Line 2, constitutes a differential system, in which cancellation of the synchronized slow components occurs and an accentuation of the asynchronous (out-of-phase) spike component takes place.

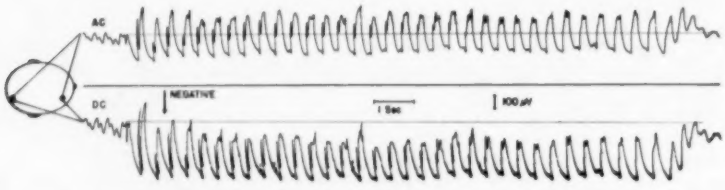

Fig. 5.—Tracing from direct-current apparatus (lower line), with ordinary condenser-coupled (A. C.) recording (upper line) for comparison. There is a maintained negative D. C. shift following the first negative spike. The negative shift persists until the cessation of spike activity.

method are shown in Figure 4. The first and third tracings record the potential differences of the homologous frontal-parietal electrode pairs; the second line records the output difference of the frontal electrodes. It is seen that the spikes, the out-of-synchrony elements, were recorded well in the transverse derivation (Line 2), whereas the almost congruent slow components were effectively canceled in this same Line 2 because of the lack of difference in potential.

In recordings of spike-dome complexes by direct-current instrumentation it was observed that a negative shift followed the first discernible negative spike discharge (lower tracing, Fig. 5). The deflection was designated as positive or negative, depending on the direction of movement of the oscillograph when the positive or negative pole of a battery was appropriately applied to "grid one" of the amplifier.

The negative shift reached maximum after two or three complexes and remained negative until the spikes were no longer present. Following the cessation of spikes, in two or three slow waves, there was a return to the A. C. characteristic of oscillating around the mechanical (and electrical) base line. In this Figure 5 ordinary A. C. recordings are shown for comparison with the direct-current tracings. In

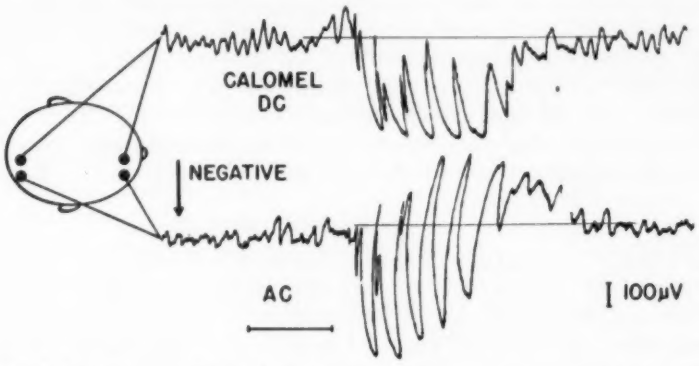

Fig. 6.—Spike-dome recording with D. C. apparatus. Direct-current recording (upper line) shows negative shift and "transient" type of recovery despite short sequence length. Ordinary A. C. recording for comparison.

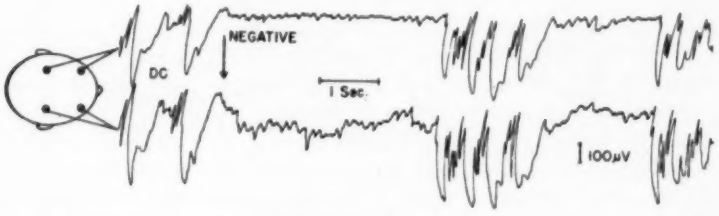

Fig. 7.—Spike-dome complexes recorded with direct-current system. Negative shifts are observed in spike-dome complexes with multiple spike components.

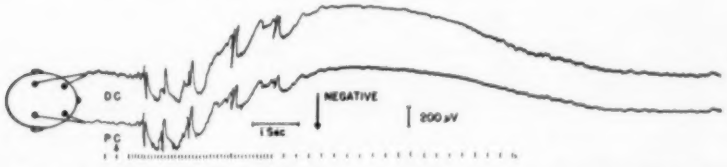

Fig. 8.—D. C. amplifier recording. Spike-dome discharge evoked by photic stimulation. The initial negative shift is overridden by the positive psychogalvanic (sweat) potential. *PC* indicates the rate of photic stimulation.

the A. C. tracing, because of the coupling condensers (or their equivalents), the spike-dome activity maintained the alternating-current property of oscillating about a fixed reference line (the drawn horizontal line), while the direct-current tracing demonstrates the maintenance of the spike-dome activity below the reference line. Each tracing, of course, was recorded from identical pairs of electrodes.

Figure 6 is similar to that of the preceding Figure. It, too, shows the transient "on-and-off" phases, despite the short sequence length of only one and one-half seconds. In the presence of multiple spikes in some spike-dome discharges, direct-current records again showed negative shifts, just as in the "classical" single spike, spike-dome complex. This is demonstrated in Figure 7. It was interesting that waves of asymmetric form, which are sometimes considered as spikes, never showed negative shifts, even when they occurred in variable short-length sequences. It also appears important to note that the asymmetrically formed waves evoked by "photic driving" did not show negative shifts with direct-current recording. Occasionally it was observed that if photic stimuli did evoke spike-dome discharges, there was a slow positive potential that overrode the negative shift (Fig. 8); this slow positive potential had the form and time characteristics of the psychogalvanic (sweat) potentials that I have earlier recorded with the direct-current apparatus.

COMMENT

The variable durations and contours of the individual spike waves of the spike-dome complexes point to the fact that one is recording from a population of neurones with differential firing capacities and thresholds.

From a theoretical point of view, the lack of precise synchronization of the spike discharges of the spike-dome complex is important. The basic idea of Jasper and Droogleever-Fortuyn[1] that there is a midline subcortical driving system responsible for the spike-dome discharge is derived from the so-called "bilateral synchrony" of these complexes, as observed in unresolved EEG tracings. In properly resolved tracings, as presented in this study, the general lack of synchrony demonstrated (5 to 20 msec.) is convincing proof that bilateral synchrony does not exist as a general phenomenon in man. Moreover, with the long latencies demonstrated there is sufficient time for relatively complex networks to be traversed. Also, with these relatively long time delays it appears evident that no direct, or common, connections can be rightfully postulated between the diencephalon and the cortex. If the diffuse diencephalic projection system, including certain thalamic nuclei, is operative in the generation of the spike-dome activity, the delays must take place in these nuclei, and not in the final projection. The argument presented here is that if the anatomically inconstant (in man) midline nuclei triggered the spikes, there should be almost precise synchronization (within 1 or 2 msec.). This is arrived at from study of direct firing systems, like that of the visual apparatus. Since the type of synchrony found in the visual system recordings is definitely not observed in the activity discussed here, any model utilizing a common excitant source appears untenable. The time delays as determined from the scalp recordings are such that the detonating potentials could arise almost anywhere in the cortical or subcortical structures. This line of argument does not prove or disprove that the primary discharges are the result of thalamic nuclei action, but the data strongly suggest that if the firing is thalamic, it is bilateral and not from nuclei common to the two cerebral hemispheres.

If there was "true" bilateral synchrony of output in the experimental work of Jasper and Droogleever-Fortuyn, which could only be proved by repeating the experiments under proper conditions, it would appear that this would be ample evidence that they were operating with a system that was not similar to the system responsible for the spike-dome activity in man.

The gross synchrony of the slow components of the spike-dome complex might indicate that a large neuronal mass is activated and that greater contiguity and synaptic effects are brought into action. It would thus appear that a proper model for the spike-dome complex is that the negative spike represents the first cortical response to subcortical, or other cortical, signals and that this discharge secondarily detonates a larger cortical mass to form the slow component of the complex.

The roughly rectangular contour of the majority of the slow elements of the spike-dome complexes lends itself to critical study. Dawson and Walter [2] have shown that the spike-dome complex can be synthesized by the in-phase addition of the 2d through the 10th harmonic when the first harmonic (fundamental) is out of phase 180 degrees. In their report these authors stated that the evaluation of the real and the "imaginary" (in a nonmathematical sense) components in this synthesis would play an important part in the determination of the mode of generation of the spike-dome complex. A detailed study of the resolved waves indicates that the aforementioned synthesis is probably a reproduction of the elements of the Fourier analysis of an idealized complex, and that the proffered synthesis does not occur in the physiological action of the neurones. This conclusion derives from the consideration that the spikes and slow components are generally not sufficiently similar (Figs. 2 and 3) to allow a precise mathematical formulation, such as was applicable to the idealized combination of a single spike and a single slow wave of equal amplitudes. Secondly, the roughly rectangular contour of the slow component, irrespective of its mode of formation, immediately disposes itself, merely because of its form, to a synthesis (or analysis) similar to that developed by Dawson and Walter. That is, the rectangular wave resulting from opening and closing a simple switch in a battery circuit would have much the same mathematical structure as that proposed by the above authors. Thirdly, in that it was shown in the D. C. recordings that multiple spike, spike-dome complexes have a negative shift similar to that observed in the single spike, spike-dome discharges, it would appear that the two types of complexes are generically related. If this is true, at least a different component mathematical series would have to be propounded to include this not uncommon case. Consequently, the fundamental concept that the spike-dome discharge is a sort of uncontrolled compounding of alpha frequency units does not appear generally valid as formulated.

The relatively gradual onset and gradual cessation of maximum negativity in the D. C. recordings act like an electrical transient superimposed on "steady-state" activity. This might indicate, in the electrical analogy, that the neurones responsible for the "steady-state" activity are different from those responsible for the spike-dome discharge.

In the direct-current recordings it must be kept clearly in mind that the D. C. shift into negativity is relative; in no way is there an attempt to relate the phenomenon to absolute values, except in the sense of battery polarity. Negative as a useful concept consists of negative with respect to a given reference. In the scalp-scalp bipolar recordings, therefore, the negativity is relative to the specific reference, the base line before and after the paroxysmal discharges. In the above sense, the spike-dome potentials recorded with the direct-current apparatus have a negative, pulsating D. C. character in that the discharge is oscillatory in nature, but remains below the mechanical (and electrical) zero line. It is rather interesting that such

paroxysmal discharges do not generate negative voltage shifts greater than 250 μv (peak value). This may be due, in part, to the shunting effect of the tissues intervening between the scalp and the brain.

Gastaut and Hunter [3] assumed, in their theoretical discussion of the spike-dome complex, that the basic contours were truly polyphasic and that the spike-dome designation was a psychological artifact. The recordings with direct-current apparatus unequivocally show that although the complexes may be considered polyphasic for convenience of notation, they are not polyphasic in the electrical sense, and are certainly not an artifact.

With the recognition of the negative D. C. shift, it now appears one can more precisely state whether evoked recruitment phenomena observed in experimental animal work have strict relationship with the human spike-dome complex. As a result of the negative shift it is no longer necessary, or sufficient, to rely entirely on morphological characteristics to determine whether a recruitment response is related to the spike-dome complex. The observed negative shift should also bring about some clarification in the clinical studies on the various contours that are fortuitously designated as spike-dome variants at the present time.

CONCLUSIONS

1. Asynchrony of appearance of the spike component of the spike-dome complex is the general observation when recording from homologous and heterologous regions of the head, if the contours are properly resolved. This asynchrony is of the order of magnitude of 5 to 20 msec. as measured from the first negative inflection.

2. Detailed study of the resolved wave forms of the spike-dome complexes indicates that a strict mathematical formulation (in terms of a Fourier series) for a physiological model is not generally applicable.

3. Recordings with direct-current instrumentation show an electrically negative shift during the generation of spike-dome discharges.

4. The hypothesis of a common nuclear projection for the formation of the spike-dome complex in man appears untenable.

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CARDIOVASCULAR RESPONSES TO EXPERIMENTAL CEREBRAL CONCUSSION IN THE RHESUS MONKEY

Discussion of Similarity of Responses to Electroconvulsive Shock and Cerebral Concussion in Dogs, Monkeys, and Man

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IN PREVIOUS papers we have reported that when the dog is used as an experimental animal the common carotid blood flow and arterial pressure responses to electroconvulsive shock and experimental concussion are similar.* Under the conditions of these experiments we inferred that the observed changes in common carotid blood flow were indicative of cerebral blood flow variations.[2] To test this hypothesis, a series of experiments were performed with electroconvulsive shock on rhesus macaque monkeys.[3] Measurement of the internal carotid blood flow in these animals indicates the status of cerebral blood flow.[4] The pattern of flow and pressure changes following electroconvulsive shock in the monkeys was similar to that obtained in dogs.[3] Furthermore, the pattern of arterial pressure responses following electroconvulsive shock therapy in psychotic patients is similar in time and direction of change to the pattern observed in dogs and monkeys after such stimuli.[5]

The present study was undertaken to obtain a direct and continuous measurement of internal carotid blood flow, arterial pressure, and cardiac rate in the rhesus macaque monkey before, during, and after delivery of a concussive blow.

EXPERIMENTAL METHODS

Mean blood flow, pulsatile blood flow, arterial pressure, and cardiac rate were recorded in the internal carotid arteries of 20 monkeys through the use of an electromagnetic blood flow meter-Statham gage-Offner recorder system.†

Surgical anesthesia was obtained in the animals by the use of alpha-chloralose, administered intraperitoneally at a dosage level of 50 to 75 mg. per kilogram of body weight. The weights of the monkeys varied from 2.5 to 5.2 kg. Alpha-chloralose, in the dosage used, does not suppress the corneal reflex, therefore the loss of the corneal reflex was adopted as one criterion of concussion.

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* References 1 and 2.

† References 2 and 6.

The surgical procedure for the cannulation of the artery has been described in detail elsewhere.[2] The combined blood flow-blood pressure pick-up was inserted into the common carotid artery. Just prior to this insertion the external carotid artery was ligated. The blood flow measured by this procedure therefore constituted a measure of the blood flow in the internal carotid artery and, inasmuch as the monkey does not have a "rete mirable" system, was accepted as an index of cerebral blood flow.[4] Blood flow and blood pressure were recorded until control values were obtained. At the end of this period a controlled blow was delivered to the occipital protuberance of the monkey's head while the animal was in a supine position. A complete description of the apparatus used to deliver the controlled blow has been published in another study.[2] Upon delivery of the blow, the durations of the resulting respiratory arrest and the abolition of the corneal reflex were timed with stop watches. Recordings of blood flow, blood pressure, and cardiac rate were continuous before, during, and after the delivery of the blow. The changes in cardiac rate were obtained from the blood pressure recordings. Recordings were continued until both blood flow and blood pressure maintained a steady state for at least 15 minutes. The flow-pressure pick-up was then removed; the artery was ligated, and the incision was sutured and dressed.

All surviving animals were kept under postoperative observation for at least 20 days. At the end of this period 10 of the monkeys that had received a concussive blow were autopsied, and the brains were examined for evidence of macroscopic or microscopic damage. The method used in fixing the brains is that described by Koenig, Groat, and Windle.[7]

RESULTS

All animals exhibited abolition of the corneal reflex and a respiratory arrest in response to a head blow. The intensity of the blow was held constant at 100 lb. per square inch in the piston. The average duration of loss of the corneal reflex was 45 seconds, with a range of from 15 seconds to 2 minutes 25 seconds. The mean respiratory arrest was 31 seconds, with a range of 10 to 45 seconds. Two of the animals exhibited convulsions of a duration of 20 and 45 seconds, respectively, immediately following the blow to the head.

Three of the animals died within seven days subsequent to the head blow. The immediate cause of death appeared to be excessive fluid in both pleural cavities, resulting in atelectasis.

After a blow to the head the mean internal carotid blood flow exhibited the following pattern of response. During the first 3 seconds subsequent to the concussive blow, mean blood flow exhibited an immediate decrease of 24% below control level; this was followed by an increase in mean flow, which reached a peak of 258% above control level by 30 seconds after the blow. By one minute following the blow the mean blood flow had decreased to a level of 119% above control. At 2.5 minutes after the blow the mean blood flow had decreased to a level of 11% above control. The decline in mean blood flow continued until six minutes after the blow, at which time the internal carotid blood flow in all animals had returned to control levels. Figure 1 is a graphical representation of these changes.

Subsequent to a concussive blow to the head, the mean arterial pressure changes in the monkey exhibited a pattern similar to the blood flow pattern. This is apparent from a consideration of Figure 1, in which both pressure and flow changes are plotted.

The maximum decrements, as well as the maximum elevations, in systolic and diastolic pressure and in blood flow occurred at approximately the same time after the delivery of a head blow. The maximum decrements below control level, in mean systolic and diastolic pressures, were 20% and 32%, respectively. The maximum

elevations above control were 70% for systolic pressure and 64% for diastolic pressure. Thereafter, there was a gradual decline in mean blood pressure until control values were reached at six minutes after a concussive blow to the head.

The cardiac rate invariably decreased immediately after a blow to the animal's head. In some cases there was actually a short-lasting cardiac arrest. After this initial decrement in mean cardiac rate an arrhythmia developed and persisted for as long as 10 minutes following the concussive blow to the head.

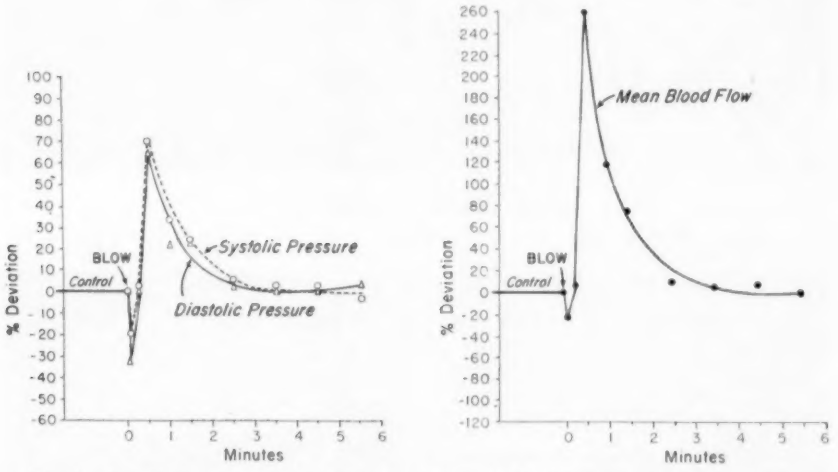

Fig. 1.—Graphical representation of the internal carotid blood flow and arterial blood pressure response of monkeys to concussion.

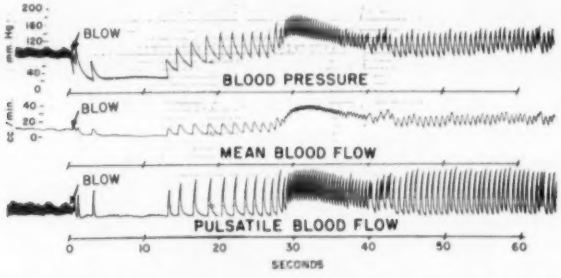

Fig. 2.—Sample record of the internal carotid blood flow and arterial blood pressure response of a monkey to concussion.

Figure 2 shows the response of one animal in this series and represents a typical record of blood flow, blood pressure, and cardiac rate responses to experimental cerebral concussion in the monkey.

Upon macroscopic examination, three of the brains exhibited small subdural hemorrhages in the superior portion of the anterior pole of the temporal lobe, just above the sphenoid ridge. In addition, all brains examined had small subdural hemorrhages in the occipital area under the point of impact of the piston delivering the concussive blow to the head.

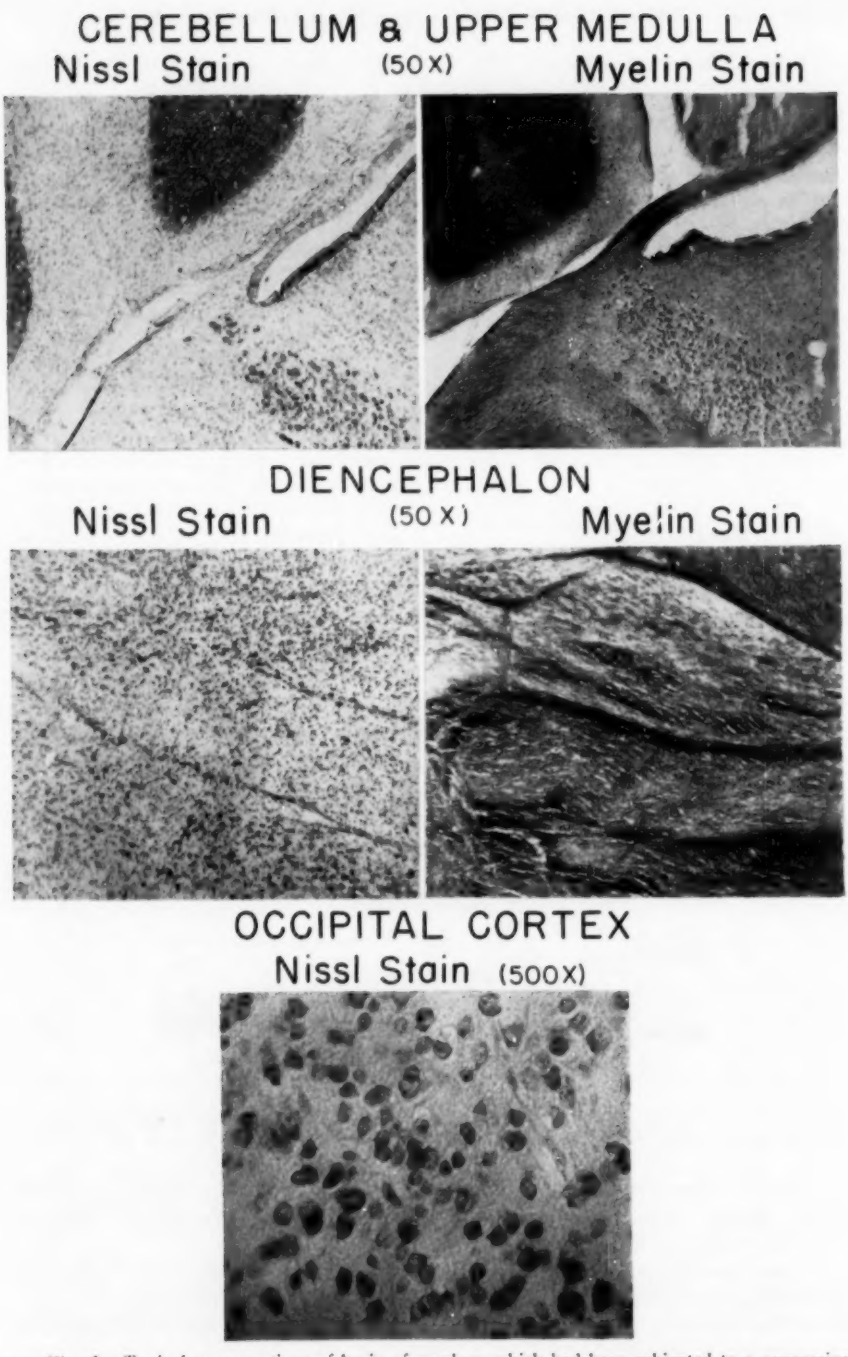

Fig. 3.—Typical cross sections of brain of monkey, which had been subjected to a concussive blow.

Microscopically, all areas of the brains appeared normal. Figure 3 illustrates representative sections of the cerebellum and the upper medulla, the diencephalon, and the occipital cortex of brains subjected to a concussive blow.

All monkeys appeared normal in their gross behavior and feeding patterns for at least 20 days before being killed.

COMMENT

An examination of the responses of man to electroconvulsive therapy and to concussive blows to the head reveals many similarities. Both phenomena produce a retrograde amnesia for the event, a respiratory arrest of variable duration, and temporary abolition of the corneal reflex; and, while convulsions do not invariably follow a concussive blow to the head, mild convulsions have been observed in association with cerebral concussion in man, monkeys, and cats.

The present study concludes a series of investigations that were designed to determine the cardiovascular responses to electroconvulsive shock ‡ in dogs, monkeys, and man and to experimental cerebral concussion in dogs [2] and monkeys. The similarity of the cardiovascular responses to both types of stimuli in all species studied is striking. After the application of either type of stimulus to dogs and monkeys and after electroshock in man, there is an initial one-to-three-second decrement in arterial pressure, followed by a marked and prolonged elevation in pressure, which returns to control levels within 10 minutes. In dogs and monkeys the cerebral blood flow follows this same pattern with respect to time and direction of change.§ Unless a different relationship between blood flow and blood pressure can be demonstrated in man than exists in dogs and monkeys, the cerebral blood flow response in man, following electroconvulsive shock, should exhibit a pattern similar to that observed in dogs and monkeys. Furthermore, since in dogs and monkeys the cardiovascular response to electroconvulsive stimulation exhibits the same pattern as the response to cerebral concussion, it is reasonable to infer that these patterns are likewise similar in man following cerebral concussion.

As a result of the evidence from our investigations of the cerebral blood flow and blood pressure responses to electroconvulsive shock and experimental cerebral concussion, we conclude that both types of stimuli act directly on the vasomotor mechanism, causing a maximal vasoconstriction in peripheral areas. The rapidity of the vasomotor response to the stimulus suggests direct central excitation, since one would expect indirect stimulation to require a longer time interval than that observed to effect the marked changes that occur. The resultant elevated blood pressure is believed to cause a passive elevation in cerebral blood flow. The evidence supporting this conclusion is that in both dogs and monkeys the elevation in cerebral blood flow is concomitant with the elevation in arterial pressure.‖ In addition, when blood flow is measured in a peripheral vessel, such as the femoral artery, there is a maximal decrease in flow occurring at the time of the maximal elevation in arterial pressure.[2] Further evidence for the central mediation of the blood pressure changes was obtained from our study of fully curarized, artificially respirated, psychotic patients subjected to electroconvulsive therapy.[5] Even in the absence of gross muscular convulsions, as in fully curarized patients, the elevation in blood pressure

‡ References 1, 3, and 5.

§ References 1, 2, and 3.

‖ References 1, 2, and 3.

following the application of electroshock was as great as that in noncurarized patients. Thus, muscular convulsions have little, if any, effect on the blood pressure patterns observed following this type of stimulus.

Scott [8] has proposed that cerebral ischemia produces the symptoms of cerebral concussion, and Davis, McCulloch, and Roseman,[9] and others have suggested that cortical anoxia may be responsible for the convulsions of electroconvulsive shock. Contrarily, it has been demonstrated by Heymans and associates [10] that interruption of the blood supply to the brain must continue for at least one minute to produce abolition of the corneal reflex. The most prolonged cardiac arrest observed in our investigations had a duration of 11 seconds in a monkey subjected to experimental cerebral concussion. In addition, a prolonged abolition of the corneal reflex occurred with a cardiac arrest of only one-second duration. Therefore, it does not seem reasonable that the short-lasting decrease in cerebral blood flow, resulting from the cardiac slowing, could account for the "loss of consciousness" accompanying concussion. We find more acceptable the proposition of Walker, Kollros, and Case [11] who hold that the "loss of consciousness" in cerebral concussion results from traumatic excitation of the nervous system.

It seems equally improbable that cortical anoxia produces the convulsion following electroconvulsive stimulation, since the time span between application of the stimulus and the onset of convulsions is too short to allow the development of anoxia of sufficient intensity to produce a convulsion. In theory, the possibility exists that cortical anoxia occurs during the convulsion, but if it does, it must occur in the presence of a greatly augmented blood supply to the brain, and the condition seems to us more likely to be subsequent, rather than antecedent, to the onset of seizure.

Our investigations do not suggest a mechanism for the production of the symptoms of cerebral concussion or electroconvulsive shock but do appear to demonstrate a striking similarity of the cardiovascular effects accompanying these stimuli. It would appear that an intense excitation of the nervous system occurs after either a concussive blow to the head or the application of electroconvulsive stimulation, and this excitation has, as one of its effects, the cardiovascular responses which we have described.

It is suggested that the anatomical differences between the skulls of dogs and of monkeys may account for the small amount of macroscopic damage observed in the monkeys, subsequent to a head blow, and for the lack of such damage in dogs.[2] In the monkey and in man the sphenoid ridge is very sharp. Any motion of the brain which would tend to force it against this sharp ridge might produce damage. On the other hand, the sphenoid ridge is practically nonexistent in the dog, being a mere smooth rounding of the skull. In addition, the monkey's skull does not have the well-reinforced external occipital ridge which characterizes the dog's skull. Thus, a blow delivered to this area of the monkey's head could more easily induce skull deformation, with resulting damage. Finally, it is possible that the subdural hemorrhages were greater in extent than might have occurred under other conditions, since the animals were highly heparinized at the time the cerebral blow was delivered.

The apparently normal behavior patterns of the monkeys prior to being killed and the absence of discernible microscopic brain damage on autopsy indicate that the macroscopic damage observed was not of a serious nature.

SUMMARY AND CONCLUSIONS

In monkeys, immediately following the delivery of a concussive head blow, there was a three-second decrease in internal carotid blood flow, arterial pressure, and cardiac rate. This response was followed by a marked and prolonged elevation in blood flow and blood pressure, accompanied by a cardiac arrhythmia. This cardiovascular response pattern in the monkey is similar to that observed in dogs, subsequent to head blows of varying intensity, and also to that following electroconvulsive stimulation applied to dogs, monkeys, and man.¶ Thus, this response pattern appears to be nonspecific, since it occurs after the application of traumatic stimuli to the head, whether electrical or mechanical in nature.

The results obtained in this series of experiments on monkeys support the conclusion drawn in the preceding series on dogs, that the "loss of consciousness" associated with cerebral concussion is not related to a diminution of cerebral blood flow.

In view of the normal gross behavior patterns, as well as the unaltered microstructure of the brain following experimental cerebral concussion, it is concluded that the blows to the head, which resulted in the abolition of the corneal reflex, produced no serious permanent damage to the brains of the monkeys used in this series of experiments.

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THE ANTERIOR CHOROIDAL ARTERY

Its Origins, Course, Distribution, and Variations

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A RECENT report (Cooper,[10] 1953) has indicated that ligation of the anterior choroidal artery in patients with paralysis agitans may ameliorate the tremor and rigidity associated with this syndrome and permit greater range of voluntary movement. Precisely why ligation of this vessel has been associated with these beneficial effects has not been answered, but it has been postulated that they probably are the result of localized ischemia and/or necrosis of portions of the globus pallidus. It has previously been determined (Carpenter, Whittier, and Mettler,[9] 1950) that localized stereotaxic lesions of the globus pallidus can ameliorate or abolish choreoid hyperkinesia in the Rhesus monkey resulting from localized lesions of the subthalamic nucleus of Luys. However, bilateral simultaneous lesions in the monkey which destroyed approximately 10% of the pallidum on each side have not been compatible with survival. It is claimed by Spiegel and Wycis * that patients with paralysis agitans are benefited by stereotaxic lesions of the pallida.

The clinical significance of the anterior choroidal artery has heretofore been considered minor. Abbie [1] (1933) reported clinicopathologically a case of bilateral occlusion of this vessel in a syphilitic patient and later [2] collected four other cases in which this vessel was occluded unilaterally. According to this author, the resulting syndrome consisted of hemiplegia, hemianesthesia (to all sensory modalities), and hemianoptic defects of varying degrees. Contralateral lesions involving the posterior two-thirds of the posterior limb of the internal capsule, the globus pallidus, parts of the optic radiations, the lateral geniculate body, and the middle third of the crus cerebri were said to have been found. The four cases collected from the literature by Abbie showed considerable variation in the extent and location of lesions.

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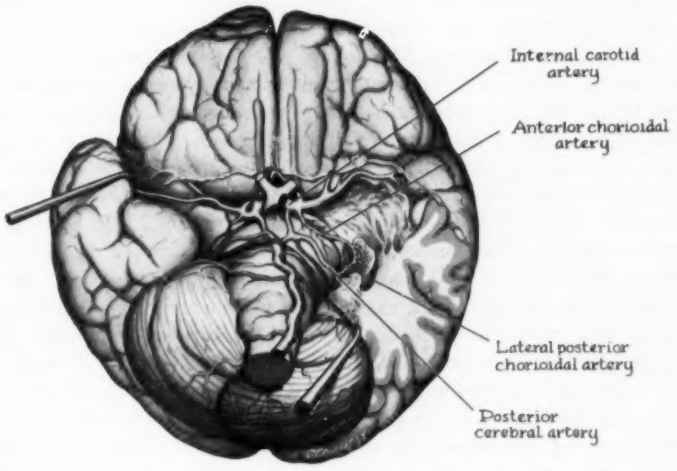
Austregesilo and Borges Fortes [5] (1933), Trelles and Lazarte [22] (1939), and Hansen and Peters [14] (1940) have reported single cases considered to have shown clinically the "syndrome of the anterior choroidal artery"; none was confirmed by autopsy. All patients exhibited unilateral sensory defects and homonymous hemianopsia, but only one had a real hemiplegia. The patient described by Hansen and Peters did not have hemiplegia and was said to have recovered spontaneously.

REVIEW OF LITERATURE

Among those investigators who have extensively studied cerebral vascular distribution, including that of the anterior choroidal artery, have been Duret, Heubner, Kolisko, Beevor, Abbie, and Alexander. All have employed various techniques of injecting fresh brains, supplemented by gross dissection. Duret [12] (1874), in his classic papers on the circulation of the brain, described the anterior choroidal artery



Drawing of a brain dissection, showing the anterior choroidal artery, the posterior cerebral artery, and the lateral posterior choroidal artery on the left. Note the anastomosis of the anterior choroidal and lateral posterior choroidal arteries.

as a terminal branch of the internal carotid artery. He mentioned its variable origin, stating that it sometimes arose from the middle cerebral artery or from the posterior communicating artery. Specific mention was made of its course along the "lateral aspect of the optic tract" and of its branches to the optic tract, cerebral peduncle, and cornu ammonis; its terminal branches were distributed to the choroid plexus of the inferior horn of the lateral ventricle. Duret did not suggest that other areas of the brain were supplied by this vessel. Heubner [15] (1874) concurred with Duret in many of his findings but, in addition, described basal branches, which were said to supply the highest part of the crus cerebri, the posterior limb of the internal capsule, and the anterior external part of the optic thalamus. According to the studies of Kolisko [16] (1891), these basal branches were found to supply only the posterior two-thirds of the posterior limb of the internal capsule below the level of the second lenticular segment (i. e., the external segment of the globus pallidus), the tail of the

caudate nucleus, the optic tract, and occasionally the superior external part of the thalamus. Beevor [6] (1908) injected multiple cerebral vessels simultaneously under the same gradual pressure with different-colored gelatin solutions. He described the anterior choroidal artery in its caudal and lateral course to the descending cornu of the lateral ventricle, where it terminated in the choroid plexus; along its course it gave off basal branches. These branches were said to supply the following structures: (1) the optic tract as far back as the lateral geniculate body; (2) the posterior two-thirds of the posterior limb of the internal capsule, as high as the superior angle of the lateral segment of the globus pallidus; (3) the internal segment of the globus pallidus and sometimes parts of the putamen; (4) the retrolenticular part of the internal capsule, including the first part of the optic radiations and the tail of the caudate nucleus (or surcingle); (5) the lateral part of the anterior commissure, and (6) the anterior one-third of the pes pedunculi. In the approximately 100 brains injected and studied by Beevor the anterior choroidal artery originated from the internal carotid artery in all cases. Abbie,† in extensive studies of the anterior choroidal artery, noted branches of this vessel, which arose near its origin from the internal carotid artery, that supplied the head of the caudate nucleus and the posteromedial border of the anterior commissure. The next group of branches were those to the pyriform cortex and uncus; the amygdaloid nucleus, hippocampus, and fascia dentata were in part supplied by these vessels. Branches to the pyriform cortex were observed to anastomose with the middle and posterior cerebral arteries, while those to the uncus and fascia dentata anastomosed with branches of the posterior cerebral artery. A series of basal branches given off more posteriorly passed medial and lateral to the optic tract, sometimes piercing it, and coursed dorsally to supply the posterior two-thirds of the posterior limb of the internal capsule, the internal segment and the medial part of the external segment of the globus pallidus, and the beginning of the optic, and probably some of the acoustic, radiations. Branches supplying the optic tract were described as passing medially and dorsally between the optic tract and the cerebral peduncle. Other branches constantly observed supplied the middle third of the crus cerebri; some of these branches passed dorsally to nourish parts of the substantia nigra, the red nucleus, and the subthalamic nucleus. Also from the main trunk of this vessel arose branches which supplied the stria terminalis and the tail of the caudate nucleus. The lateral half of the lateral geniculate body constantly received its blood supply from the anterior choroidal artery. Abbie remarked, concerning the variations of origin of this vessel, that he had seen all variations of origin (i. e., from the internal carotid, middle cerebral, and posterior communicating arteries) except for its complete absence. He felt that the results and conclusions of his injections studies were closely confirmed in his one case of bilateral occlusion of this vessel. Alexander [4] (1942) found that injection of the anterior choroidal artery usually resulted in staining of the entire medial and intermediate segments and parts of the lateral segment of the globus pallidus (in 25% of his cases the entire pallidum except the anteroventral tip of its lateral segment was stained), the ventral part of the posterior limb of the internal capsule with the adjacent proximal parts of the optic and acoustic radiations, part of the tail of the caudate nucleus and the adjoining posteroventral crest of the putamen, the anterior part of the lateral geniculate body, the uncus, the cornu ammonis, and parts of the

† References 1 and 2.

amygdaloid nucleus. Parts of the substantia innominata and the posterolateral dorsal portions of the optic tract were also stained. No statistical information concerning the various origins of the anterior choroidal artery was given.

The sites of origin of the anterior choroidal artery, as given in 27 standard anatomical texts and monographs in three languages, were checked. In 22 of these this vessel was stated to arise from the internal carotid artery exclusively. In two texts the vessel was said to have come from the middle cerebral artery; one mentioned origins from either the internal carotid or the middle cerebral artery. Only two texts mentioned possible origins from the internal carotid, the middle cerebral, or the posterior communicating artery, and these gave no indication of the frequency of such origins.

TABLE 1.—*Sources of Material Used in This Investigation*

Source	Brain No.	Right Hemisphere	Left Hemisphere	Both Hemispheres
1. Anatomy Laboratory, Columbia University College of Physicians and Surgeons	A-3	X	..	..
	B-2	..	..	X
	B-4	..	..	X
	B-5	..	..	X
	B-6	..	..	X
	D-4	X	..	..
	D-5	..	..	X
	D-6	..	..	X
2. Rockland State Hospital, Orangeburg, N. Y.	Autopsy No.			
	2067	..	..	X
	2070	..	..	X
	2071	..	X	..
	2072	..	..	X
	2079	..	X	..
	2178	..	..	X
3. New Jersey State Hospital, Greystone Park, N. J.	Autopsy No.			
	A368	..	..	X
	A479	..	..	X
	A554	X	..	..
	A556	..	..	X
	A564	X	..	..
	A565	..	..	X
	A567	..	..	X
	A568	..	..	X
	A570	..	..	X
	A576	..	..	X
	A580	..	..	X
	A584	..	..	X
	A587	..	..	X
4. New Jersey State Hospital, Marlboro, N. J.	Autopsy No.			
	A2072	..	..	X
	A2074	..	..	X
	A2075	..	..	X
	A2077	..	..	X
	A2078	..	..	X
	Unknown	..	..	X

PRESENT STUDY

Material and Methods.—This investigation was based on the study of 60 hemispheres of 33 formalin-fixed brains, obtained from the anatomy laboratory of the Columbia University College of Physicians and Surgeons; the Rockland State Hospital, Orangeburg, N. Y., and the New Jersey State Hospitals at Greystone Park and Marlboro, N. J. The number of brains from these sources and the hemispheres studied are recorded in Table 1. None of the brains examined

was known to have come from a patient with paralysis agitans. Dissections of the anterior choroidal artery were made of all brains obtained from state hospitals. Diagrams of the vessel, its branches, and course were made in each case. The posterior cerebral artery was dissected in part, and the course and distribution of the lateral posterior choroidal artery were studied and drawn in 45 hemispheres. None of the vessels of these brains were injected.

Results.—The anterior choroidal artery originated from the internal carotid artery in 76.6% of these hemispheres, from the middle cerebral artery in 11.7%, from the posterior communicating artery in 6.7%, and from the junction of the anterior and middle cerebral arteries in 3.3%. The internal carotid artery was considered to terminate at the point where the anterior cerebral artery was given off. In one hemisphere (1.7%) the anterior choroidal artery was absent. In 90% of the 48 hemispheres in which the anterior choroidal artery arose from either the internal carotid artery or the junction of the anterior and middle cerebral arteries, it was the first branch given off after the posterior communicating artery; it was the second branch in 2 hemispheres, the third branch in 2 hemispheres, and the fourth branch

TABLE 2.—*Measurements* of the Points of Origin of the First Branches of the Anterior Choroidal Artery*

Distance of First Branch from Origin of Vessel, Mm.	No. of Hemispheres
At origin	3
1	5
2	4
3	2
4	6
5	7
6	4
7	6
8	2
9	1
10	3

* Forty-two measurements.

in 1 hemisphere. The posterior communicating artery was absent in 3 of these 60 hemispheres. Branches given off from the internal carotid artery prior to the anterior choroidal artery were perforating branches which entered the anterior perforated substance with the "lenticulostriate" vessels. The anterior choroidal artery was given off lateral to the optic tract in all but 2 hemispheres (97% of hemispheres) and crossed the optic tract first from lateral to medial, and then from medial to lateral, in 51 hemispheres (85%). In two hemispheres the anterior choroidal artery remained lateral to the optic tract throughout its course; in one instance it arose lateral to the optic tract, which it crossed four times, ending lateral to it. In two hemispheres the vessel arose from the internal carotid artery medial to the optic tract and crossed it once from medial to lateral. At its origin the vessel measured 0.6 to 1 mm. in outside diameter; in a few instances it was considerably smaller than this. The point at which the first branch was given off from the anterior choroidal artery was measured in 42 hemispheres, and the results are recorded in Table 2. The length of the vessel from its origin to its entrance into the choroid plexus of the inferior horn of the lateral ventricle (57 measurements) ranged from 15 to 35 mm. and averaged 26 mm.

THE ANTERIOR CHOROIDAL ARTERY

The principal branches of the anterior choroidal artery were found to be (*a*) perforating branches, (*b*) branches to the uncus, (*c*) branches to the cerebral peduncle, (*d*) branches to the optic tract and lateral geniculate body, and (*e*) terminal branches to the choroid plexus. Perforating branches arose from the parent artery throughout its course and were the first branches given off from the anterior choroidal artery in 26 hemispheres. Many of these rami entered the anterior perforated space with the lateral striate vessels from the middle cerebral artery. Uncal branches were long and slender and usually came off from the parent vessel at a right or an obtuse angle and pursued a straight course. This branch was the first given off from the anterior choroidal artery in nine hemispheres and was seen in all brains. The fine caliber of this branch and its concealed position rendered preservation during dissection difficult. Branches which entered the cerebral peduncle were usually given off after the anterior choroidal artery had crossed the optic tract; these were very fine and multiple. Branches to the optic tract originated throughout the course of the vessel and varied in length, caliber, and number. Some of the branches passed directly into the optic tract, while others passed around it into the substance of the brain. In the region immediately in front of the lateral geniculate body the rami ran on the surface of the optic tract caudally toward the lateral geniculate body. Other branches were given off to the lateral geniculate body, usually on its lateral aspect, by the anterior choroidal artery prior to its entrance into the choroid plexus. Anastomoses between the anterior choroidal artery and the lateral posterior choroidal artery, a branch of the posterior cerebral artery, occurred either rostral to the lateral geniculate body or over the surface of that structure or at both sites in 36 of the 45 hemispheres in which the latter vessel was dissected. The lateral posterior choroidal artery anastomosed directly with the anterior choroidal artery rostral to the lateral geniculate body in 3 hemispheres and with the anterior choroidal artery via the choroid plexus in 38 hemispheres. The lateral posterior choroidal artery was absent in four hemispheres.

COMMENT

It would appear that the anterior choroidal artery arises from the internal carotid artery in most instances as the next branch after the posterior communicating artery. It may, however, arise from the middle cerebral artery, from the junction of the middle and anterior cerebral arteries, from the posterior communicating artery, or it may be absent in rare cases. Certain confusion regarding its origin has arisen because of inconsistent nomenclature. This difficulty seems to surround the definitions of the internal carotid artery and the middle cerebral artery. We have considered the internal carotid artery as terminating at the point where the anterior cerebral artery is given off (Cunningham,[11] 1951). Abbie has stated that the anterior choroidal artery arises from the internal carotid artery, but his illustration (Fig. 4 [1]) reveals the vessel originating distal to the place where the anterior cerebral artery arises (i. e., from the middle cerebral artery).

Anastomoses between the branches of the anterior choroidal artery and the posterior choroidal artery have been specifically mentioned by numerous authors. Duret termed these vessels posterolateral and posteromedial choroidal arteries, stating that they entered the choroid plexus of the lateral and third ventricles, where anastomoses occurred. Beevor [7] mentioned communications between the anterior and

posterior choroidal arteries and remarked he had found it easy to inject that portion of the choroid plexus usually supplied by the anterior choroid artery by injection of the posterior cerebral artery. The reverse, injection of the anterior choroidal artery, did not always fill the portion of the choroid plexus usually supplied by the posterior choroidal artery. Poirier and Charpy [20] found that injected material from the anterior choroidal artery rapidly entered the posterior cerebral artery, indicating an effective anastomosis via the posterior choroidal artery. Godinov,[13] in a study of 100 brains, found anastomoses between the anterior choroidal artery and (1) the posterior communicating artery, (2) branches of the interpeduncular plexus, and (3) the posterior choroidal artery. Abbie ‡ has repeatedly stated that the anterior and lateral posterior choroidal arteries anastomose in the choroid plexus of the lateral ventricle and over the surface of the lateral geniculate body. According to this author, the blood supply of the lateral geniculate body is fairly constant, the lateral segment being supplied by branches from the anterior choroidal artery, the medial segment by branches from the posterior choroidal artery, and the "intervening region, which corresponds to the hilum of the nucleus, is nourished through a rich anastomosis from both sources." Anastomoses between the anterior and posterior choroidal arteries are also mentioned by Quain [23] (1909), Tandler,[21] Piersol,[19] Belou,[5] Padget,[18] and Cunningham.[11]

Bilateral fulguration of the anterior choroidal arteries (done in two separate stages one month apart) in a normal adult chimpanzee (Mettler and associates,[17] 1954) did not result in lesions comparable in extent or location to those described by Abbie as constituting the terminal field of supply of this vessel. Resulting necrosis was asymmetrical, involving adjacent portions of both internal and external pallidal segments near the internal medullary lamina. It has been hypothesized that this particular type of failure, termed "subtotal terminal failure," occurs in that part of the primary distribution of a vessel in which overlap or anastomosis with surrounding vessels is minimal or nonexistent. The work of Mettler and his colleagues suggests that the posterior limb of the internal capsule, although it is within the primary zone of distribution of the anterior choroidal artery, must also receive an additional supply by means of overlap or anastomosis, probably from the posterior communicating artery. This hypothesis has been borne out in pathologic examination in human cases of ligation of the anterior choroidal artery, in which the effects have varied from necrosis of the apical portions of the pallidum to no obvious structural defect (Mettler and associates [17]).

Information concerning the anastomoses of the anterior choroidal artery in the "normal" state indicates that this vessel, except for its terminal rami, is not an end-artery in the Cohnheim sense. It would seem that isolated thrombosis of this vessel or single emboli to it would not result in extensive necrosis in its primary field of supply if surrounding and anastomotic vessels were normal. Likewise, ligation of this vessel in its "normal" state should not be attended by necrosis of an extensive nature, except insofar as the mechanism of ligation is accompanied by trauma and the propagation of thrombi, factors which are difficult or impossible to control. In the case of a diseased vasculature, which is what the surgeon is dealing with in a case of paralysis agitans (whether arteriosclerotic or postencephalitic), it would seem

‡ References 1, 2, and 3.

that the resulting ischemia and/or necrosis would be unpredictable as regards location and extent. These uncontrollable factors add to the surgical risk involved in performance of this procedure.

SUMMARY AND CONCLUSIONS

An investigation was made of the anterior choroidal artery, based on the study of 60 hemispheres of 33 formalin-fixed brains obtained from state hospitals and an anatomy laboratory. None of these brains was known to have come from a patient who had paralysis agitans. This vessel was found to originate from the internal carotid artery in 76.6% of the hemispheres, from the middle cerebral artery in 11.7%, from the posterior communicating artery in 6.7%, and from the junction of the anterior and middle cerebral arteries in 3.3%. The anterior choroidal artery was absent in one hemisphere. When the anterior choroidal artery arose from the internal carotid artery, it was usually the next branch after the posterior communicating artery. The vessel usually originated lateral to the optic tract, which it crossed twice, entering the substance of the brain lateral to the lateral geniculate body. Its caliber varied from 0.6 to 1 mm., and its length averaged 26 mm. The principal branches of the anterior choroidal artery were (*a*) perforating branches, (*b*) branches to the uncus, (*c*) branches to the cerebral peduncle, (*d*) branches to the optic tract and lateral geniculate body, and (*e*) terminal branches to the choroid plexus of the inferior horn of the lateral ventricle.

Anastomoses determined by gross dissection were found between the anterior choroidal artery and the lateral posterior choroidal artery in 42 of 45 hemispheres in which the latter vessel was dissected. Such anastomoses occurred over the surface of the optic tract and lateral geniculate body and in the choroid plexus.

The hypothesis is presented that the anterior choroidal artery in its "normal" state is not an end-artery, except in its small terminal rami.

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NEUROPATHOLOGIC FINDINGS IN DISSEMINATED LUPUS ERYTHEMATOSUS

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DISSEMINATED lupus erythematosus has come to be understood as a "collagen disease" in which there exists widespread systemic alteration of connective tissue. The fundamental lesion is one involving the smaller arteries, wherein degeneration of the subendothelial connective tissue produces homogeneous eosinophilic fibrinoid material. This substance may then extend into the lumen of the blood vessel, inducing thrombosis and consequent infarction of the parenchymal tissue.

A review of the subject * indicates that etiologic concepts of the condition have remained speculative and diverse. For example, Klemperer [6] reported recently that histochemical investigation of acute lupus erythematosus disclosed disturbance in metabolism of nucleic acid as one of the pathogenetic factors. On the other hand, Brody [7] found that psychologic stress situations seem a consistent factor in the precipitation or exacerbation of the disease.

Central nervous system manifestations, in view of the vascular nature of the disease, are widespread, as may be gathered from a recent review by Sedgwick and Von Hagen [8] and from our Table. Despite the appearance of numerous clinical reports since Kaposi [9] first described the disease, there is a marked paucity of neuropathologic investigations.

Our purpose, therefore, is to report the postmortem findings in three cases in which the central nervous system was involved and to evaluate these in the light of a review of previously reported studies.

REPORT OF CASES †

CASE I.—A. F., a white woman aged 43, was first hospitalized in the neuropsychiatric clinic in January, 1950, because of mental confusion and emotional instability. There was a history of a positive Wassermann reaction in 1938, reportedly followed by adequate treatment. On admission, the patient's conversation was rambling, but her orientation and memory were good and there were no psychotic manifestations. Physical and neurologic examinations revealed questionable Oppenheim and Gordon signs on the left. The Wassermann test of the blood was positive, but that of the spinal fluid was negative. The spinal fluid contained 13 leucocytes per

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The statements published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the United States Air Force.

* References 1 through 6.

† The staffs of Agnews and Stockton State Hospitals supplied the material used in this study.

cubic millimeter and a total protein of 47 mg. per 100 cc. and showed a colloidal gold curve of 1112110000. An electroencephalogram revealed a focus of mildly abnormal slow activity in the right posterior temporal area. The patient was discharged after one week of hospitalization, since the presenting symptoms had apparently cleared spontaneously.

Two months later she was admitted to a state hospital with symptoms diagnosed as schizophrenic reaction, mixed type. The only significant findings at that time were mild hypertension and a colloidal gold curve of 2221000000 for the spinal fluid. She again improved without specific treatment and was discharged in November, 1950.

One year later, in December, 1951, the patient was admitted to a county hospital because of marked confusion, disorientation and memory defect, rapid mood swings, rambling speech, and paranoid ideation. A diagnosis of "dementia praecox with paranoid tendencies and deterioration" was made, and she received six weeks of ambulatory insulin therapy, consisting of 70 treatments, without improvement. There developed rapidly thereafter an erythematous rash on the nose, cheeks, and palms; pain, swelling, and tenderness of joints; albuminuria; elevation of blood pressure to 190/140; a systolic cardiac murmur, and flame-shaped hemorrhages and exudates in the fundi. It was only then that the diagnosis of disseminated lupus erythematosus was established, to which the mental symptoms were attributed.

She was committed to a state hospital in March, 1952, for further care, and there received 20 electroshock treatments, which eventually had to be discontinued because of increasing severity of signs of nephritis. The patient gradually became more lethargic, expressed auditory hallucinations, was unable to swallow, and went into congestive heart failure in October, 1952. She received 100 mg. of cortisone daily from that day to Nov. 7 but became progressively more emaciated and edematous and died on Nov. 30, 1952.

Necropsy.—The significant findings were lupus erythematosus; acute fibrinous pericarditis, acute bacterial endocarditis involving the mitral valve, and fatty degeneration of the myocardium; chronic glomerulonephritis, and hyperplasia of the spleen.

The brain weighed 1,250 gm. Macroscopically, it showed a "granular atrophy" of the cerebral cortex, characterized by myriad retracted scars and moth-eaten lesions affecting symmetrical areas on the lateral surface of the frontal, parietal, and occipital lobes (Fig. 1). The leptomeninges were thickened in these regions, but the blood vessels were not remarkable. Coronal sections revealed an irregularly narrow and spongy cortex in the affected areas and moderately enlarged ventricles.

Microscopically, the lesions showed a characteristic pattern of miliary infarcts. They were equally numerous in the cerebral and cerebellar gray matter but were rare in other parts of the central nervous system. They were wedge-shaped and varied from acute ischemic necrosis to subacute softening, to chronic gliosis (Fig. 2). They corresponded, respectively, to lesions of arterioles, which varied from acute fibrinoid degeneration of subendothelium associated with hemorrhagic thrombi to chronic thickening, hyalinization, and fat infiltration of the wall, with organized thrombi undergoing secondary recanalization (Fig. 3).

Case II.—A. K., a Negro girl aged 17, was admitted to a county hospital in February, 1952, with a rash of two months' duration on her face, hands, and ankles. Past history was negative. Examination revealed a "mentally sluggish," acutely ill girl. Temperature was 101.4 F., pulse rate 100, respirations 18, and blood pressure 112/60. There was a butterfly distribution of erythema on the bridge of the nose, with superimposed keratotic plaques and a rose-colored eczema of the palms and soles. The patient demonstrated generalized weakness of all extremities. The blood contained 10 gm. of hemoglobin (67%) and 3,750,000 red cells and 3,000 white cells, with a differential count of 46% polymorphonuclear leucocytes and 64% lymphocytes. The urine gave a 2+ reaction for albumin. The corrected erythrocyte sedimentation rate was 40 mm. in one hour. Wassermann test of the blood was negative, and the nonprotein nitrogen was 24 mg. per 100 cc.

The patient received cortisone therapy for two and a half months, with little improvement. It was discontinued in mid-April, 1952, because of development of mental depression, which progressed to a frank psychosis, during which she was belligerent, defecated upon the floor, and refused to remain clothed.

She was then committed to a state hospital, where she was found to be dehydrated, confused, disoriented, and noncommunicative. Physical examination showed fuzzy rings in the iris, depig-

mentation and scarring of the face, and spotty alopecia of the scalp; neurologic examination was not remarkable. Two electroshock treatments were administered, with some improvement in the mental condition. This treatment was discontinued, however, as the patient became increasingly toxic, with a temperature of 102 F., pulse rate of 140-160, generalized body pain, and

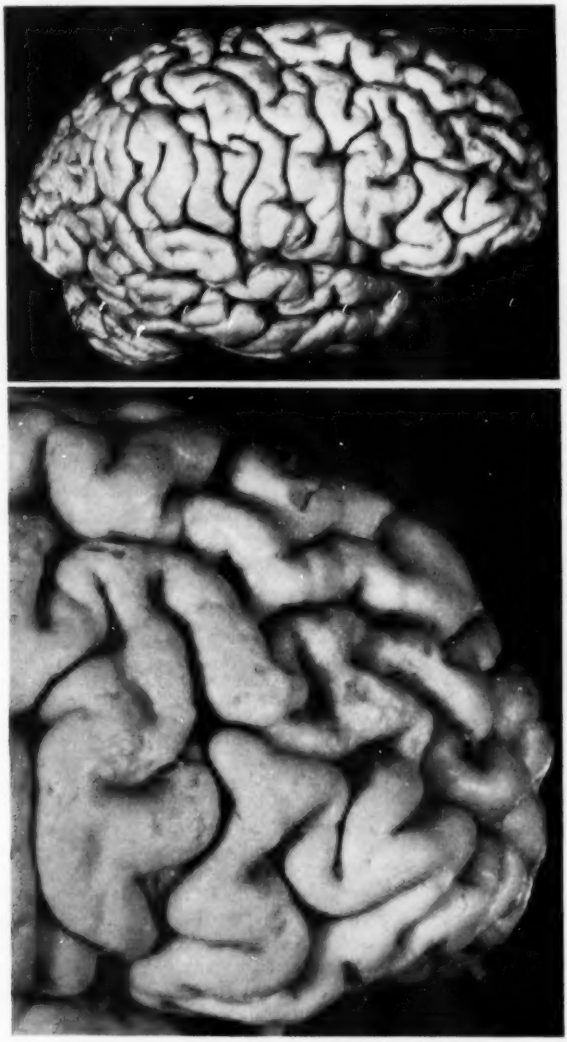

Fig. 1 (Case I).—Gross appearance of brain, showing focal "granular atrophy" of the cerebral cortex.

increasing number of skin lesions. During the last five days she had several grand mal convulsions, became stuporous, finally lapsing into coma, and died on May 25, 1952.

Necropsy.—Evidence of disseminated lupus erythematosus was disclosed, but there were no further details.

Grossly, the brain weighed 1,265 gm. and was not remarkable. Microscopically, arterioles in the meninges, and less commonly within the brain substance, showed eosinophilic fibrinoid deposits in the subendothelium, which tended to extend into the rest of the wall of the blood vessel (Fig. 4*A*). There were also fat-containing vacuolated cells in the subendothelium, and some blood vessels contained fibrin thrombi, but none were organized. There were occasional infiltrations of the leptomeninges with polymorphonuclears and lymphocytes. Miliary infarcts were seen in the nerve tissue which were directly related to the vascular lesions (Fig. 4*B*). These lesions were invariably acute, consisting of necrosis of the tissue, ischemic changes in neurons, and variable proliferation of microglia and macroglia. In general, neither the vascular nor the parenchymal lesions were numerous, but they were widely scattered in the cerebral cortex, white matter, thalamus and cerebellum, and one pyramidal tract.

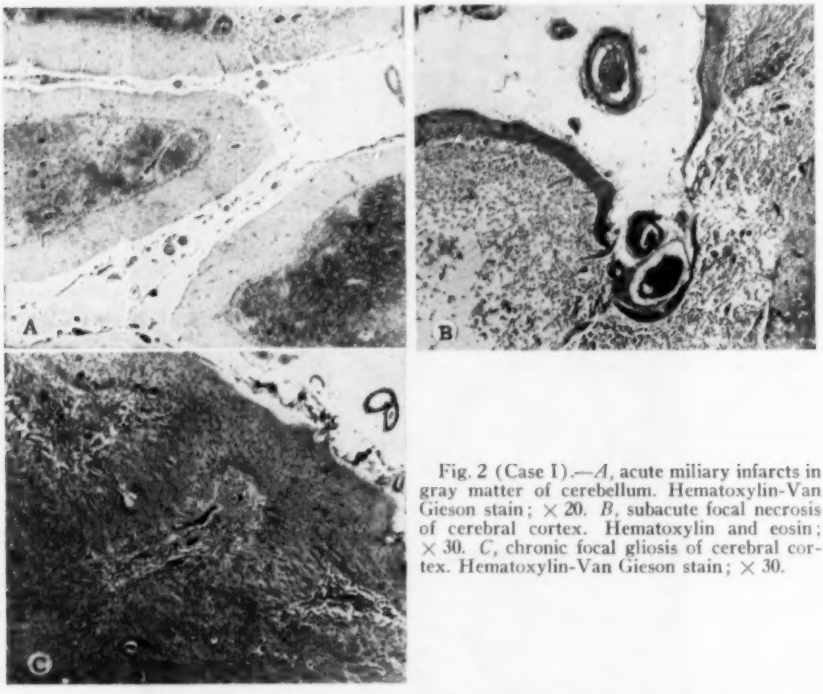

Fig. 2 (Case I).—*A*, acute miliary infarcts in gray matter of cerebellum. Hematoxylin-Van Gieson stain; × 20. *B*, subacute focal necrosis of cerebral cortex. Hematoxylin and eosin; × 30. *C*, chronic focal gliosis of cerebral cortex. Hematoxylin-Van Gieson stain; × 30.

Case III.—E. B., a white woman aged 33, was admitted to a state hospital in December, 1951. She had a lifelong history of emotional instability. In 1946 she underwent a splenectomy for "idiopathic" thrombocytopenic purpura. The following year, after the development of a rash and a cardiac murmur, the diagnosis of disseminated lupus erythematosus was made. In 1951 she was treated for 23 weeks with corticotropin, until December, at which time she became agitated and depressed, expressed auditory hallucinations and suicidal ideas, and was committed to a state hospital.

Physical examination revealed an undernourished, weak woman, weighing 99 lb. (44.9 kg.) and showing old brownish skin blotches on the face and body. There were severe tachycardia and a systolic murmur. Neurologic examination was negative. A psychiatric diagnosis of catatonic schizophrenia was made, and she received 10 electroshock treatments in January, 1952, with marked improvement. In February she developed a bilateral pleural effusion, which cleared with treatment within a month. She was then transferred to the county hospital for continuation treatment of the lupus and was discharged home in May, 1952. She had been on cortisone

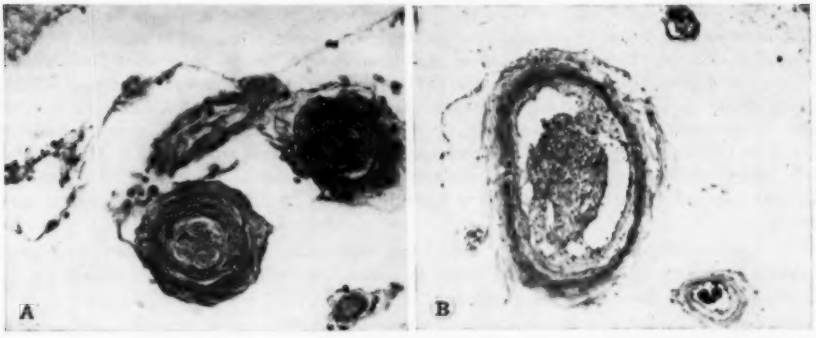

Fig. 3 (Case I).—*A*, acute fibrinoid degeneration and thrombosis of meningeal arterioles of cerebellum. Hematoxylin-Van Gieson stain; × 120. *B*, chronic sclerosis and recanalized thrombosis of small meningeal artery of cerebral cortex. Hematoxylin and eosin; × 60.

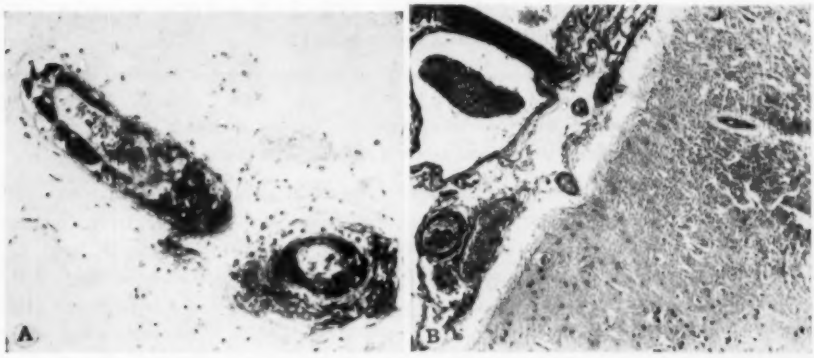

Fig. 4 (Case II).—*A*, acute fibrinoid degeneration of small meningeal arteries of cerebral cortex. Hematoxylin and eosin; × 60. *B*, acute anemic infarct of cerebral cortex associated with thrombosis of small meningeal arteries. Hematoxylin-Van Gieson stain; × 60.

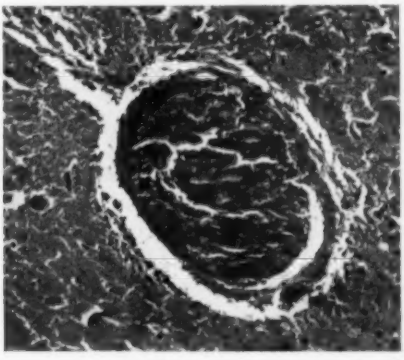

Fig. 5 (Case III).—Acute thrombosis and perivascular anemic necrosis of small artery in thalamus. Hematoxylin and eosin; × 90.

therapy (½ tablet [12.5 mg.] every eight hours) during 1952 and remained well. Early in 1953, however, she began to show increasing depression, necessitating readmission to the state hospital in March, 1953. Examination at this time showed her to be oriented and without delusions or hallucinations, but withdrawn, and she realized that she needed treatment. Weight was now 130 lb. (59 kg.). Neurologic examination was again negative. Laboratory findings, with the exception of slight albuminuria, were not remarkable. The patient was treated with 75 mg. of cortisone daily and received four electroshock treatments from April to May 5, 1953, with improvement. On May 6, 1953, she suddenly collapsed while brushing her teeth, fell backward and struck her head, causing a large hematoma of the right parieto-occipital area, and died.

Necropsy.—The essential findings were lupus erythematosus, acute coronary thrombosis, resulting in myocardial infarction and mural thrombosis, and chronic adhesive pleuritis.

The brain was not remarkable grossly.

Microscopically, a few scattered arterioles within the cerebral cortex, thalamus, and putamen showed fibrosis, at times associated with acute thrombosis and perivascular necrosis (Fig. 5).

COMMENT

Our cases demonstrate that involvement of the central nervous system in lupus erythematosus varies greatly. On the basis of our findings and those reported in the literature, the following syndromes may be classified:

A. Specific organic brain syndrome, resulting from the basic vascular lesions of either acute or chronic type (as in our Cases I and II)

B. Nonspecific toxic encephalopathy, due to such complications as uremia

C. "Functional" disorders with minimal cerebral pathology, as in our Case III

We found in the literature 17 cases of disseminated lupus erythematosus with involvement of the central nervous system that have been subjected to histopathologic study‡ (Table). Of these, eight (Cases 5, 7, 9, 13, 14, 15, 16, and 17) presented the pathognomonic vascular lesions and fit into our classification of the specific organic brain syndrome. Cases 10 and 12 are examples of a nonspecific acute toxic encephalopathy without the typical vascular lesions. The remaining seven cases are more difficult to classify by virtue of incomplete description. Six of them (Cases 1, 2, 4, 6, 8, and 11) showed such changes as congestion, hemorrhage, or thrombosis without evidence of the specific vascular lesions. One wonders, however, if they really deserve separate classification or if a more thorough investigation might not have revealed the basic lesion. The only case of meningoencephalitis in the series is mentioned by Keil (Case 3), and since it has not been further described, evaluation is difficult.

But while the above classification is warranted, there is reason to believe that in many instances the organic and functional factors are combined in varying degree. In Case I, the severe cerebral pathology was without doubt alone responsible for the neuropsychiatric symptoms throughout the patient's progressive course of three years' duration. It is of interest that this patient showed no response to either insulin or electroshock treatment. In Case II, however, in which the organic brain syndrome predominated, the psychosis, which was apparently exacerbated by a course of cortisone therapy, was temporarily improved with E. C. T. Particularly in Case III, however, in which the brain changes were minimal, a "functional" disorder dominated the clinical picture, a classification which was further confirmed by the improvement with each course of E. C. T.

‡ References 10 through 22.

Clinicopathologic Data in Seventeen Cases of Disseminated Lupus Erythematosus from the Literature

Case	Author	Symptoms		Neuropathologic Findings
		Neurologic	Psychiatric	
1	Tremaine [10] 1934	N. R.*	N. R.	Subarachnoid hemorrhages
2	Jareho [11] 1936	N. R.	None	Areas of encephalomalacia in cerebral cortex and in cornu ammonis; many thrombosed cerebral vessels
3	Keil [12] 1940	N. R.	N. R.	Meningoencephalitis
4	Cluxton and Krause [13] 1943	Recent headaches, vertigo, diplopia, blurred vision, bilateral sustained ankle clonus, hyperactive deep reflexes, muscle tremors	.....	Moderate atrophy of cerebral cortex; perivascular "atrophy" in basal ganglia; perivascular hemorrhages in pons
5	Daly [14] 1945	Recent headaches, muscle twitching of extremities, aphasia	Terminal confusion and disorientation	Typical vascular changes with corresponding acute and chronic parenchymal lesions
6	Lian and others [15] 1947	Terminal clonic convulsions, nuchal rigidity, increased knee reflexes, divergent strabismus, and oculogyric crises	None	Large area of encephalomalacia; vascular congestion and thrombosis
7	Tumulty and Harvey [16] 1949	Terminal left-sided Jacksonian seizures and hemiplegia; coma	None	Subdural and intracerebral hemorrhage in left occipital lobe; typical vascular lesions
8	Tumulty and Harvey [16] 1949	Terminal choreiform movements	Periodic, erratic behavior; terminal delirium and stupor	Old and recent petechial hemorrhages in brain
9	Bauer and others [17] 1950	Chorea, ataxia, asynergy, and weakness preceding appearance of lupus and then subsiding	Initial emotional lability, progressing to terminal psychosis	Typical vascular lesions and infarcts of cerebral cortex and lenticular nuclei
10	Vesey and Nelson [18] 1950	Increasing drowsiness for 5 mo.; bilateral nonsustained ankle clonus, terminal convulsions	Terminal disorientation	Extensive neuronophagia and chromatolysis; vascular congestion
11	Brunsting and others [19] 1951	Negative	Premorbid compulsive guilt feelings, becoming worse with cortisone therapy	Petechiae of brain
12	Russell and others [20] 1951	Terminal convulsions	Terminal confusion	Diffuse perivascular infiltrations and edema
13	Russell and others [20] 1951	Terminal coma	Terminal cloudy sensorium	Perivascular hemorrhage of internal capsule; typical vascular lesion in one pontine vessel
14	Glaser [21] 1952	Negative	Terminal irrational state and uremia	Multiple foci of encephalomalacia of cerebral cortex associated with vascular lesions
15	Glaser [21] 1952	Convulsions for 4 mo. prior to death; terminal spasticity of right and flaccidity of left extremities; convulsion and coma	Early convulsions preceded by "raving, confused, agitated state"; mental depression	Acute and chronic encephalomalacia of cerebral cortex, hippocampus, corpus striatum, thalamus, and stem, with typical vascular lesions
16	Glaser [21] 1952	Negative	Disorientation and delirium in last 16 days	Hemorrhagic encephalomalacia of cerebral cortex and many typical vascular lesions
17	Piper [22] 1953	One month prior to death; ascending weakness, numbness, and tingling of lower extremities and trunk, difficult micturition; hypoactive reflexes; decreased pinprick sensitivity perianally; left positive Babinski sign; terminal generalized twitching	None	Petechial hemorrhages in right basal ganglia; infarction of lumbar cord due to thrombosis of meningeal vessels; myelomalacia of posterior funiculi; typical vascular lesions

* N. R. indicates not reported.

That symptoms referable to the central nervous system may actually mark the onset of disseminated lupus erythematosus is illustrated in Case I. Here, the organic cerebral manifestations were noted a full two years before the appearance of cutaneous lesions and the recognition of the disease entity. Similarly, Bauer and associates [17] and Glaser [21] reported cases in which episodes of "Sydenham's chorea" preceded the rash by six weeks to one year, respectively. Brunsting and associates [19] described a patient who sought psychiatric treatment six months prior to the appearance of other symptoms. Vesey and Nelson [18] observed a patient with increasing fatigability and drowsiness five months before eruption of the lupus rash. Russell, Haserick, and Zucker,[20] in reporting patients who had convulsions for years prior to the appearance of recognizable symptoms of lupus erythematosus, suggest that epilepsy, when accompanied by rheumatoid arthritis or leucopenia, may constitute a prodromal symptom of systemic lupus.

One might raise the question of whether hormonal therapy, in the form of corticotropin and cortisone, can by itself induce clinical symptoms based on underlying changes in the central nervous system. Glaser and Merritt [22] report convulsions occurring during hormone treatment, as do other authors.§ But since convulsions are among the commonest neurologic manifestations of the disease, Brunsting [19] quite rightly points out that such complications are not unusual where corticotropin and cortisone are not given. He also reports a frequent masking of lupus symptoms by such hormones. We encountered this difficulty in the evaluation of the psychiatric symptoms in our Cases II and III, which seemed to accompany both the hormone therapy and the underlying disease. Castor and associates [24] report chromatolysis in the cells of the paraventricular nuclei of the hypothalamus of rats treated with corticotropin, and more widespread changes in the thalamus and hypothalamus with cortisone therapy. Such changes, however, could not be found in our cases, even though in Case III a prolonged course of corticotropin and cortisone therapy was given. In regard to the effectiveness of hormonal therapy, Soffer and associates [25] and O'Leary and Erickson [26] point out that, although hormones are capable of inducing remissions, a cure of the underlying disease process is not effected. In our Cases I and II the disease progressed rapidly in spite of cortisone therapy, but in Case III there were periodic remissions with combined hormone treatment.

SUMMARY

1. Clinicopathologic studies are reported of three cases of disseminated lupus erythematosus with involvement of the central nervous system.

2. The cases are classified in the light of a tabulated review of similar studies in the literature under (*a*) specific organic brain syndrome; (*b*) nonspecific toxic encephalopathy, and (*c*) "functional" disorders with minimal cerebral pathology.

3. The difficulty of evaluating the neuropsychiatric symptoms when corticotropin or cortisone therapy is used in this disease is briefly discussed.

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PERITHELIAL SARCOMA OF THE BRAIN

A Clinicopathological Study of Thirteen Cases

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DURING the past 25 years there has developed an increasing interest among neuropathologists in primary intracranial sarcomas. There has, in general, been agreement concerning the diagnosis of diffuse sarcomatosis of the meninges, melanomatosis of the meninges, and meningeal and intracerebral fibrosarcoma. However, the interpretation of those types of sarcoma which Bailey [1] described in 1929 as perithelial and alveolar has been extremely varied, and at present several different concepts exist. From our clinical and pathological study of 13 cases that have been diagnosed as perithelial sarcoma in the Montreal Neurological Institute since 1936, we have concluded that the types previously termed perithelial and alveolar probably represent variations of a single entity. It is with this neoplasm, which we have continued to designate by the well-established term perithelial sarcoma, that this report is concerned.

REVIEW OF LITERATURE

An increasing number of reports * of primary intracranial sarcomas have appeared during recent years, and several excellent reviews † of the older literature are available. We should like to summarize briefly those articles which have proved most helpful in organizing and interpreting our material.

Bailey [1] in 1929 attempted to clarify the position of sarcomas among the primary intracranial neoplasms. He felt that these tumors originated from the leptomeninges over the surface of the brain or from the perivascular extension of the leptomeninges, which he termed perithelium, surrounding the penetrating blood vessels. He described four types of neoplasms: perithelioma, perithelial or perivascular sarcoma, fibrosarcoma, and alveolar sarcoma. Bailey presented two cases classified as peritheliomas and described several others in the literature. He characterized this type of neoplasm as a rather slowly growing tumor involving the leptomeningeal and perivascular spaces, either locally or diffusely, whose cells had not broken through the pia glia membrane, and suggested that they perhaps were not true sarcomas. Two cases of perithelial or perivascular sarcoma were described, each of which was located in the temporal lobe of a middle-aged man. Both tumors were

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* References 2 through 10.

† References 1, 11, and 12.

composed of round cells, and the closely packed perivascular arrangement was accentuated by intervascular necrosis. Mitotic figures were frequent. Reticular fibers were seen scattered among the neoplastic cells. Bailey felt that the concentric rings of reticulin surrounding the blood vessels and separated by tumor cells were characteristic of intracranial sarcomas, either primary or metastatic, and that the reticulin was formed by the neoplastic cells. Two cases of fibrosarcoma were presented, one of which grossly was thought to be a meningioma. Bailey described one case as one of alveolar sarcoma, occurring deep in one cerebral hemisphere of a 5-year-old boy, but did not know whether the tumor was primary or metastatic. It was partly degenerated, but the visible cells were round or irregular, arranged in alveolar structures which were separated by connective tissue septa. A perivascular arrangement of neoplastic cells was seen only in the adjacent cerebral tissue which was invaded.

In 1938 Yuile [13] reported a case of primary intracranial sarcoma which he thought was identical with the two cases described by Bailey [1] as cases of perithelial sarcoma. This was a deep infiltrating neoplasm within the central portion of one hemisphere in a 50-year-old man. The cells were 6 to 10 μ in diameter, had heavy chromatin particles with prominent nucleoli, and showed numerous mitotic figures. The cells were closely packed in the perivascular spaces, spreading out into less cellular areas, in which there were heavy fibrous deposits. Reactive astrocytes and numerous macrophages were scattered throughout the tumor. The walls of many of the blood vessels had been invaded by the tumor cells. With appropriate stains coarse reticular strands were demonstrated, closely associated with tumor cells surrounding the blood vessels. Yuile, however, felt the reticulin bore no direct relationship to the neoplastic cells, since numerous areas of tumor farther from the vessels contained no reticulin. With Hortega's silver carbonate method for microglia, most of the tumor cells were well stained, showing considerable variations in shape and in types of processes. Yuile classified this tumor as a primary reticulum cell sarcoma of microglial origin.

Bailey, Buchanan, and Bucy [14] separated five cases in their series of malignant tumors of the cerebellum in childhood from the medulloblastomas, calling them perithelial sarcomas, alveolar sarcomas, or leptomeningeal sarcomas on the basis of the perivascular arrangement of cells and the distribution of reticulin.

Hsü [11] in 1940 concluded that primary tumors in the brain which reproduced the structure of sarcomas elsewhere in the body probably arose from the leptomeningeal tissue either over the surface of the brain or around its blood vessels. In addition to diffuse sarcomatosis of the meninges and fibrosarcoma, he recognized both perithelial and alveolar types of sarcoma. In the one case of perithelial sarcoma which he described, there was a large rapidly growing neoplasm within the left temporoparietal region of a 9-year-old boy, who died three months after operation and x-ray therapy. The perivascular cellular arrangement within the tumor was accompanied by marked intervascular necrosis. Invasion had occurred by both direct extension and extension along perivascular spaces. Reticulin fibers were present both about vessels and scattered among the neoplastic cells. One alveolar sarcoma was described, occurring within the fourth ventricle of a 26-year-old woman who survived two years after the initial operation and a course of x-ray therapy. No perivascular cellular arrangement was noted within the tumor, which had a

mesenchymal appearance and whose cells, with oval nuclei, were separated into alveolar structures by strands of reticulin. No description was given of the method of invasion into the surrounding cerebellum.

Abbott and Kernohan [12] in 1943 reported 12 cases of primary sarcoma of the brain which they felt could be divided into two main types: the fibrosarcomas and the perivascular or perithelial sarcomas. The fibrosarcoma was considered to be histologically identical with the malignant "stromal" type of meningioma. They concluded that this type of meningioma [15] (malignant, fibrous, sarcomatous) differed from the primary fibrosarcoma in its gross appearance only in that it occurred on the surface of the brain, with subsequent invasion of the underlying nerve tissue, whereas the primary fibrosarcoma occurred primarily within the brain. These authors would include under the term "fibrosarcoma" those cases previously reported as reticulum cell sarcoma, alveolar sarcoma, reticuloendothelioma, retotheliosarcoma, and *sarcome primitif*. In two of their three cases of fibrosarcoma there was definite perivascular arrangement of the neoplastic cells, and in one there was perivascular invasion of adjacent cerebral tissue.

In the same article Abbott and Kernohan [12] reported seven cases of perivascular sarcoma, which they divided into the following types, depending upon the diffuseness of invasion in the perivascular and leptomeningeal spaces: perivascular or perithelial sarcoma (Group A), diffuse sarcomatosis (Group B, Type 1), diffuse perivascular sarcoma (Group B, Type 2), and true diffuse leptomeningeal sarcomatosis (Group C). In all of their cases the tumors occurred in males between the ages of 17 and 57 years, with short histories of a few weeks or months. All patients died, five being operated upon; the survival time varied from six weeks to seven months after onset of symptoms. Three tumors occurred in the cerebellum, three occurred in the cerebral hemisphere, and one was present in the right lateral and fourth ventricles. The gross pathology of these sarcomas ranged from a localized mass with a pseudocapsule of degenerated and invaded brain tissue to a diffuse neoplastic process involving the major portion of one or both hemispheres. Microscopically the tumors were densely cellular with relatively small, round or oval, occasionally somewhat spindle-shaped, cells with hyperchromatic nuclei and a scant to moderate amount of finely granular, poorly stained cytoplasm. There was only a moderate degree of pleomorphism, but mitotic figures were frequent. There were numerous small blood vessels scattered in varied interconnecting patterns throughout the tumors. Reticulin was found intimately associated with the neoplastic cells. Perivascular multiple rings of reticulin were seen in each case. Sections through the border of the tumors showed neoplastic spread through the Virchow-Robin spaces, and tumor cells could be seen in intimate contact with, and apparently budding off, the adventitia of the cerebral vessels. On numerous occasions neoplastic cells were observed growing from the vessel walls both into the Virchow-Robin spaces as well as into the lumen of the vessel. In one case they observed tumor cells growing out of the walls of the smallest capillaries, which they felt precluded the origin of the tumor from the pia mater, since it had been shown by Schaltenbrand and Bailey [16] that the pial sheaths did not extend so far along the cerebral vessels. Abbott and Kernohan, therefore, concluded that the perivascular sarcomas probably arose from connective tissue within or surrounding the walls of the cerebral vessels.

Kinney and Adams [17] in 1943 reported two cases of primary intracranial sarcoma, which they classified as reticulum cell sarcomas. They felt that these two tumors were identical with five other cases in the literature variously diagnosed as cases of perithelial sarcoma,‡ microglioblastoma,§ and reticuloendothelioma.[19] All tumors had occurred in males between the ages of 9 and 72 years, and all had been relatively discrete neoplasms involving one temporal lobe. The clinical signs and symptoms had been remarkably similar, and the total survival period ranged between 1 and 16 months. Complete autopsy on each patient had excluded other lesions in the body. The microscopic appearance of the tumors was quite uniform, being composed of cells resembling histiocytes 12 to 14 μ in diameter. Numerous cells differentially stained as microglial phagocytes or macrophages were present. A delicate stroma of reticulum surrounded individual cells and groups of cells in their two cases, and reticulum was noted as abundant in each of the other five cases cited. The neoplastic cells were arranged in a perivascular pattern in all tumors, with frequent invasion of vessel walls. Kinney and Adams felt that these tumors were all identical with reticulum cell sarcomas found elsewhere in the body. They believed that the reticulin was not produced by the neoplastic cells but was derived from fibroblasts which had been activated by the presence of the neoplastic cells. On the basis of silver carbonate stains in their two cases, they concluded that, while large numbers of microglial elements were present, the majority of the neoplastic cells were not impregnated by the metallic stain. They, therefore, favored the theory that this type of intracranial sarcoma arose, not from the meningeal or perithelial histiocyte or the microglia, but from their common progenitor, the primitive reticulum cell. It is interesting that Bailey considered the tumor in their second case to be identical with the neoplasm reported by Hsü [11] as an alveolar sarcoma.

Russell, Marshall, and Smith [20] in 1948 reported seven cases of focal tumor-like proliferations in the brain, which they designated by the term microgliomatosis. In four of these cases the lesions were confined to the central nervous system, while in three cases there were similar proliferations in other organs, such as lung, spleen, lymph nodes, parotid gland, kidney, and bone marrow. There were four males and three females, with ages varying from 15 to 47 years. Death occurred two or three months after the onset of symptoms. Neither ventriculography nor operation was performed on these subjects. At autopsy each showed single or multiple ill-defined areas of infiltration in the cerebrum, basal ganglia, brain stem, or cerebellum. The neoplasm had a soft, gray-white or yellowish homogeneous appearance but sometimes contained areas of hemorrhage, necrosis, or caseation. Microscopically the tumors were found to be cellular, with no particular pattern within the neoplasm but with definite perivascular invasion of surrounding neural parenchyma. Mitosis was frequently seen. Lymphocytes, plasma cells, and microglial cells, in varying degrees of differentiation, were identified as the cells comprising the neoplasms. On the basis of specific silver impregnation techniques they recognized three types of lesions: 1. In the first type there was a proliferation of microglial cells of the mature resting type, both diffusely spread in the cerebral tissue and also forming dense focal accumulations. 2. In the second type of lesion two cell forms occurred in different areas of the brain, but in any one area one type of cell was predominant.

‡ References 1 and 11.

§ References 13 and 18.

The first cell type was identical with that seen in the first group, being a well-stained adult microglial cell with many branching processes. The second cell type had a large spheroidal nucleus which was less intensely stained by silver and showed less development of their branching processes, thereby approaching more the ameboid form. 3. The third type of lesion was most commonly observed, and in these a smaller proportion of the cells were stained by the silver techniques and resembled resting or ameboid microglia, while a larger proportion of the cells showed a lesser amount of silver in their cytoplasm, producing various shades of black and gray. The authors concluded that these feebly impregnated cells represented anaplastic or dedifferentiated histiocytes. A variable increase in reticulin fibrils was present in all the tumors. It was felt that the cells spreading within the perivascular spaces frequently split the normal layers of reticulin surrounding the vessels without actually

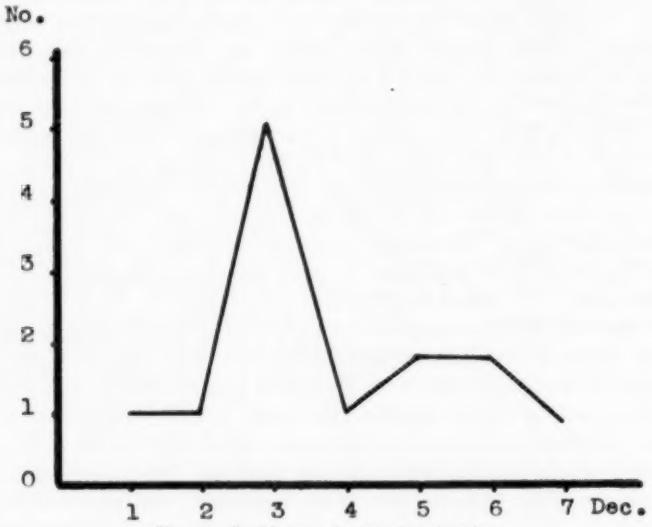

Fig. 1.—Incidence of cases by decades.

increasing the amount of reticulin. In some areas of the neoplasm there seemed to be an increase in diffuse reticulin fibrils, but in general they did not feel this was a dominant feature.

Russell and co-workers [20] felt that the tumors which they described as microgliomas were the same as those reported by other authors,[18] including the reticulum cell sarcomas presented by Yuile [13] and Kinney and Adams.[17] They suggested that many of the tumors reported by other workers as peritheliomas, perithelial sarcomas, perivascular sarcomas, and alveolar sarcomas also would fall into the category of microgliomas if special silver-staining techniques had been employed.

CLINICAL SUMMARY

Age.—The ages of the 13 patients in this series varied from 9 to 63 years, with an average of 35 years. Five cases occurred during the third decade, two cases in the fifth and sixth decades, and one case in the first, second, fourth, and seventh decades (Fig. 1).

Sex.—While several authors have mentioned that this type of tumor was found practically always in males, this series is almost equally divided between the sexes, seven being in males and six in females.

Duration of Symptoms (Table 1).—The time from the onset of symptoms until the date of admission to this hospital varied between two weeks and nine years, with an average of about two years. Case 8, in which a slowly progressive left hemiplegia

TABLE 1.—*Clinical Data on Thirteen Cases of Perithelial Sarcoma of the Brain*

Case	Age, Yr.	Sex	Duration of Symptoms	Location of Tumor	Operation	X-Ray Treatment	Postoperative Survival
1	42	M	3 yr.	Frontal	Yes	Yes	Died 6 mo.
2	9	F	2 yr.	Occipital	Yes	Yes	Died 6 mo.
3	35	F	2 wk.	Fronto-temporal	Yes	Yes	Died 4 mo.
4	22	M	6 wk.	Frontal	Yes	Yes	Died 6 mo.
5	43	M	3 yr.	Parietal	Yes	Yes	Died 5 mo.
6	24	F	2½ yr.	Cerebellar	Yes	Yes	Died 21 mo.
7	26	F	1½ yr.	Cerebellar	Yes	Yes	Alive 48 mo.
8	53	M	9 yr. (?)	Parietal	Yes	No	Died 1 mo.
9	16	F	3 yr.	Temporal	Yes	No	Died 5 mo.
10	63	M	2 yr.	Temporal	Yes	No	Died 18 mo.
11	59	M	2 mo.	Parieto-occipital	Yes	Yes	Died 5 mo.
12	22	F	4 mo.	Cerebellar	Yes	Yes	Alive 13 mo.
13	29	M	5 mo.	Cerebellar	Yes	Yes	Alive 3 mo.

TABLE 2.—*Symptoms and Signs in Thirteen Cases of Perithelial Sarcoma*

Presenting Symptoms at Entry		Positive Findings on Examination	
Headache	12	Papilledema	12
Nausea and vomiting	10	Motor weakness	5
Unsteady gait	5	Unilateral hyperreflexia	5
Fatigability	4	Apathy	4
Impaired vision	4	Drowsiness	3
Focal seizures	3	Impaired memory	3
Drowsiness	3	Extensor plantar response	3
Dizziness	3	Diplopia	3
Unilateral weakness	3	Nystagmus	3
Apathy	2	Ataxia	3
Poor memory	2	Hemianopsia	2
Anorexia	2	Impaired sensation	2
Double vision	2	Diminished visual acuity	1
Confusion	2	Vertigo	1
Irritability	2	Confusion	1
Photophobia	1	Anisocoria	1
Thick speech	1	Dysarthria	1

had developed nine years prior to admission was a complicated case in which a frontoparietal head injury had been sustained 33 years previously. Until two months before admission to this hospital he had had no signs of increased intracranial pressure and three separate pneumoencephalograms had shown evidence of an atrophic lesion in the right parietal area, where at operation a deep-seated neoplasm was found. If this case is omitted, the duration of symptoms in the other 12 cases varied from two weeks to three years, with an average duration of 18 months.

Presenting Symptoms (Table 2).—Headache was the commonest symptom, being present in all but one of the cases, and nausea and vomiting had occurred

in 10. Five patients gave a history of an unsteady gait. Fatigability and impaired vision were each complained of by four patients. Focal cerebral seizures, drowsiness, dizziness, and unilateral weakness were each noted in three of the cases. More rarely, the patients or their families described apathy, impaired memory, anorexia, diplopia, confusion, irritability, photophobia, or dysarthria.

Signs on Examination (Table 2).—Of the 13 patients, all except one showed papilledema on examination. This was usually bilaterally present and quite marked. Some form of motor weakness was found in five patients, either as varying degrees of hemiparesis or as weakness of both legs. Unilateral hyperreflexia was noted in five instances. Four patients showed apathy. Drowsiness and impaired memory were each noted in three patients. A unilateral Babinski sign, diplopia, nystagmus, and ataxia were each recorded in three instances. Hemianopsia, impaired sensation, diminished visual acuity, vertigo, confusion, anisocoria, and dysarthria were infrequently encountered.

Clinical Diagnosis.—There was no characteristic clinical entity represented among these 13 cases which might serve to identify tumors of this type. In each

TABLE 3.—*Location of Thirteen Cases of Perithelial Sarcoma of the Brain*

Cerebral	9
Frontal	2
Temporal	2
Parietal	2
Occipital	1
Frontotemporal	1
Parieto-occipital	1
Cerebellar	4
Left hemisphere	3
Left hemisphere and vermis	1

instance, however, sufficient symptoms and signs were present to enable one to make a diagnosis of an expanding intracranial lesion, to locate it above or below the tentorium, and usually to lateralize the neoplasm correctly. In no case was there suggestive clinical evidence of disease elsewhere in the body.

Laboratory and Diagnostic Procedures.—No significant abnormality was found in the examination of the blood. Except for one case with albuminuria, urinalysis disclosed no abnormality. Blood Wassermann reactions were negative in all cases. Lumbar cerebrospinal fluid was obtained for study preoperatively in only four cases. In each instance the cerebrospinal fluid protein was elevated above normal. In one case there were 16 lymphocytes per cubic millimeter, and in another case the Lange gold curve showed an elevation in the midzone.

Skull x-rays were obtained in all 13 cases and were considered normal in 6 of them. Decalcification of the dorsum sellae was noted as a sign of increased intracranial pressure in two cases. A calcified pineal gland was found to be shifted in four patients, and there was pathological calcification in the occipital lobe of one case (Case 2). X-ray examination of the chest showed no significant abnormality in any of the cases. A pneumoencephalogram or, more frequently, a ventriculogram was performed in 12 of the 13 cases and led in each instance to a correct localization of

the neoplasm. Electroencephalography was carried out preoperatively on four patients, in three of whom the lesion was accurately localized. In one case of a temporal neoplasm (Case 9) the localization was inaccurate.

Location of Tumors (Table 3).—In nine cases, the neoplasm was located in the cerebral hemispheres. There were two tumors in the frontal lobe, two in the temporal lobe, two in the parietal lobe, and one in the occipital lobe. One neoplasm was frontotemporal in location, and another was parieto-occipital. Four tumors

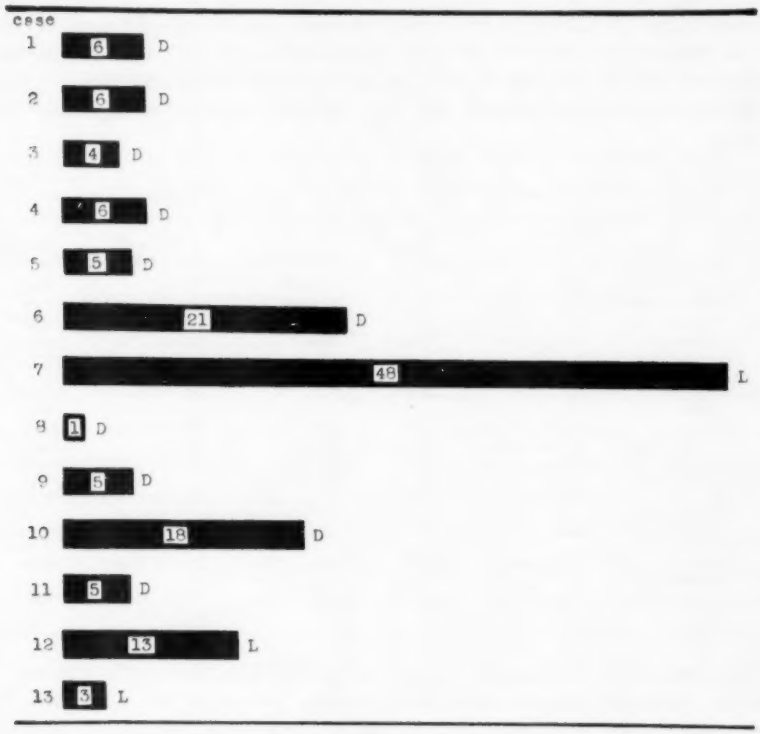

Fig. 2.—Postoperative survival, in months, of 13 cases of perithelial sarcoma of the brain.

were present in the posterior fossa, three being in the left lateral hemisphere of the cerebellum, and one being in the left cerebellar hemisphere and vermis. While postmortem examination was available in only one case (Case 8), there was no clinical, x-ray, or operative evidence of either multiple intracranial neoplasms or extracranial lesions.

Surgical Therapy.—All of the 13 patients were operated upon. No patient died during operation or in the immediate postoperative period. In each instance there was evidence of increased intracranial pressure, which was marked in three cases. What was thought to have been grossly a complete tumor excision was accomplished in about one-third of the cases.

X-ray Therapy (Table 1).—Ten patients received postoperative x-ray therapy restricted to the region of the neoplasm. In all but one case (Case 12) this treatment was given in the Royal Victoria Hospital in Montreal, and the therapy was fairly well standardized during the past 10 years.

Results of Therapy (Fig. 2).—Of the 13 patients operated upon, 10 are now dead. Their survival time ranged from 1 to 21 months, with an average of 7.7 months. The three patients who were operated upon but who did not receive x-ray therapy (Cases 8, 9, and 10) are all dead. Their survival periods were 1, 5, and 18 months, respectively, with an average survival of 8 months. Three patients are living and well (Cases 7, 12, and 13), having survived now 4 years, 13 months, and 3 months, respectively. All three of these patients had neoplasms in the left cerebellar hemisphere, and in only one instance (Case 12) was it thought that a complete excision had been accomplished. All these patients received postoperative x-ray therapy.

TABLE 4.—*Gross Pathologic Data on Thirteen Cases of Perithelial Sarcoma*

Case	Gross Form	Color	Consistency	Degeneration	Meningeal Involvement	Ventricular Involvement
1	Circumscribed	Red, brown	Tough	Necrotic	None	None
2	Circumscribed	Pink, yellow	Firm	Necrotic	None	None
3	Circumscribed	Gray, white	Firm	Cystic	None	None
4	Circumscribed	Gray, yellow	Tough	None	None	None
5	Nodular and diffuse	Pink, fleshy	Soft	None	None	None
6	Nodular and diffuse	Red, gray	Firm	None	Pia-arachnoid	Fourth ventricle
7	Diffuse	White, yellow	Soft	None	Pia-arachnoid	None
8	Circumscribed	White, gray	Firm	None	None	None
9	Partially circumscribed	Yellow, brown	Soft	Necrotic hemorrhagic	None	None
10	Partially circumscribed	Gray, yellow	Firm	Hemorrhagic	Pia-arachnoid	None
11	Partially circumscribed	Red, yellow	Tough	None	Pia-arachnoid and dura	Subepend. lat. vent.
12	Partially circumscribed	Gray, yellow	Soft	Necrotic	Pia-arachnoid	None
13	Circumscribed	Gray, white	Soft	Cystic	Pia-arachnoid and dura	None

Eight patients were thought to have been significantly improved as the result of operation, although this beneficial effect usually proved to be temporary. Five patients were worse after surgery. One patient developed a persistent dysphasia, and three had a permanent hemiplegia postoperatively. Atelectasis, persistent fever (thought to have been secondary to blood in the cerebrospinal fluid), and focal seizures each occurred in a single instance, and all the patients responded to conservative measures. In one case (Case 8), deepening coma developed and the patient died one month postoperatively. There were no postoperative hemorrhages or infections.

PATHOLOGICAL SUMMARY

Gross (Table 4).—At operation, in 6 of the 13 cases the tumor appeared on the surface of the brain, this being true in all instances where the tumor was located in the cerebellum. In seven cases the tumor was located deep in the cerebral hemispheres, but in all the six cases where the tumor presented on the surface there was extension also into the white matter. In 11 cases the ventricles were not

involved, but in 1 case there had been extension to the wall of the lateral ventricle. In one other case a nodule of tumor protruded into the fourth ventricle. The leptomeninges grossly were involved in all six cases where the neoplasm presented on the surface, and in two cases the tumors had become adherent to the dura. Often it was difficult to determine whether the tumors had arisen from single or from multiple foci. In eight cases, because of the existence of single large nodules or masses, it was assumed that origin had occurred from a solitary focus. In two cases multiple nodules were present and connections between them could not be established definitely. In the remaining three cases the mode of origin could not be decided. The consistency of these neoplasms varied considerably, but they tended to be firm. In four cases they were quite firm, even rubbery, while six others were firmer than brain. The remainder were soft. In seven instances the predominant color of the tumor was grayish-yellow to white, while in six cases the tissue was

TABLE 5.—*Microscopic Pathologic Data on Thirteen Cases of Perithelial Sarcoma*

Case	Mitoses	Pattern	Inter-vascular Necrosis	Invasion	Connective Tissue	Glia in Tumor
1	Frequent	Perivascular alveolar	Yes	Perivascular	Abundant	Astrocytes
2	Infrequent	Perivascular alveolar	Yes	Perivascular	Abundant	Microglia
3	Infrequent	Perivascular alveolar	Yes	Perivascular	Moderate	Microglia
4	Infrequent	Perivascular dense sheets	Yes	Perivascular	Abundant	.....
5	Frequent	Perivascular dense sheets	Yes	Perivascular leptomeningeal	Moderate	Microglia Astrocytes
6	Infrequent	Perivascular alveolar	No	Perivascular leptomeningeal	Moderate	.....
7	Infrequent	Perivascular dense sheets	No	Perivascular leptomeningeal	Moderate	Microglia Astrocytes
8	Frequent	Perivascular dense sheets	Yes	Perivascular	Abundant	Microglia Astrocytes
9	Infrequent	Perivascular alveolar	No	Perivascular	Abundant	Microglia Astrocytes
10	Frequent	Perivascular dense sheets	Yes	Perivascular leptomeningeal	Abundant	Microglia Astrocytes
11	Infrequent	Perivascular alveolar	No	Perivascular leptomeningeal	Abundant	Microglia Astrocytes
12	Infrequent	Perivascular alveolar	No	Perivascular leptomeningeal	Abundant	Microglia Astrocytes
13	Infrequent	Perivascular alveolar	Yes	Perivascular leptomeningeal	Moderate	Microglia

described as being pink, red, or fleshy in appearance. Three tumors seemed to be well localized, with a definite frontier between neoplasm and brain. All of these were located in the cerebrum. Usually the border consisted of a zone of yellow, necrotic nervous tissue, and there was never any evidence of true encapsulation. Two of the four tumors occurring in the cerebellum were partly localized, but in general these neoplasms were diffusely invasive. Some degeneration or hemorrhage into the tumor substance was usual, and in two cases there were cysts.

Microscopic (Table 5).—The single most striking histological characteristic of these tumors was the perivascular arrangement (Fig. 4*A*) or extension of the neoplastic cells (Fig. 3*A-D*), this being a prominent feature in all 13 cases. Within solid nodules or masses of neoplasm this propensity to spread in the perivascular spaces could not always be recognized because the cells were arranged in sheets or cords (Fig. 4*B, D*). However, examination of the brain adjacent to the tumor

for the most part revealed numerous small vessels surrounded by cuffs of tumor cells. In some instances the neoplastic cells were located in or on the walls of arterioles or capillaries, as if their origin were integrally related to cells in these

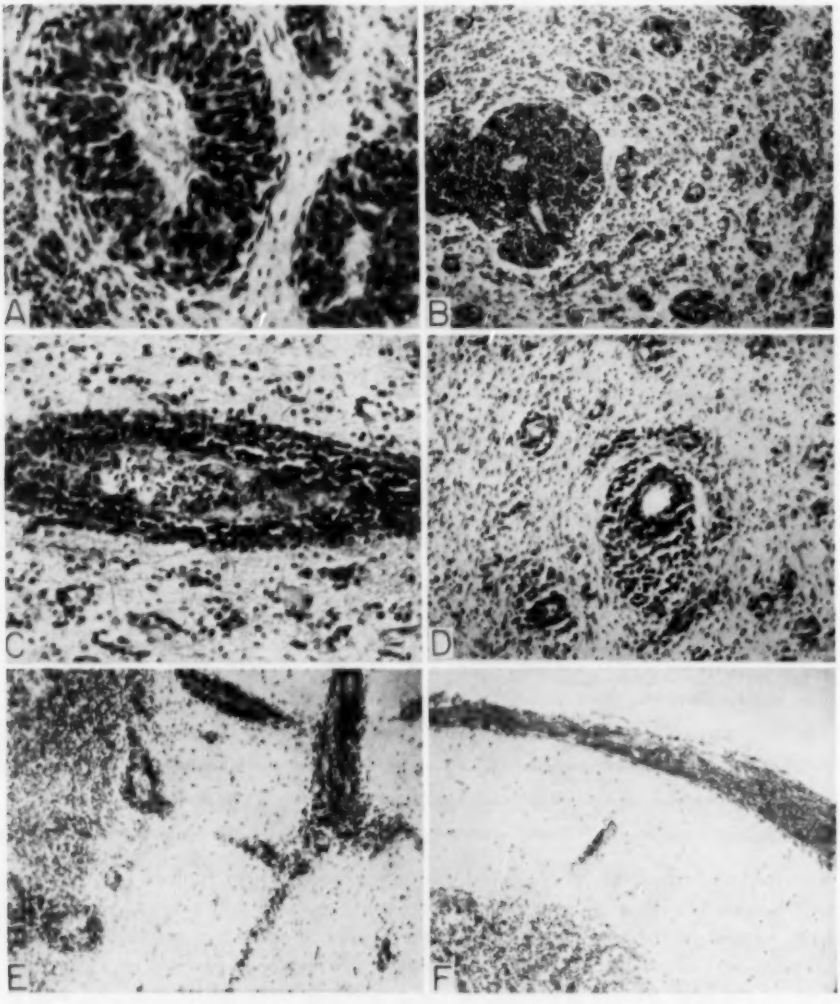

Fig. 3.—Perivascular invasion of neoplasm. *A*, Case 7. Hematoxylin and eosin; × 200. *B*, Case 10. Hematoxylin and eosin; × 80. *C*, Case 10. Phosphotungstic acid hematoxylin; × 195. *D*, Case 9. Cresyl violet; × 93. Leptomeningeal and perivascular invasion in the cerebellum. *E*, Case 7. Hematoxylin and eosin; × 81. *F*, Case 6. Hematoxylin and eosin; × 91.

walls. Still more rarely, there were groups of neoplastic cells within the lumina of small vessels, as if they were "budding" off the walls.

Spread of the neoplasm in the subarachnoid space or by infiltration of the leptomeninges occurred in seven cases. Where this was found in the cerebellum, the

spaces between several folia would be filled with tumor, and from this area invasion of cerebellar tissue would take place along the perivascular spaces (Fig. 3*E*, *F*).

An alveolar-like pattern was found in six cases, and in three of these it was

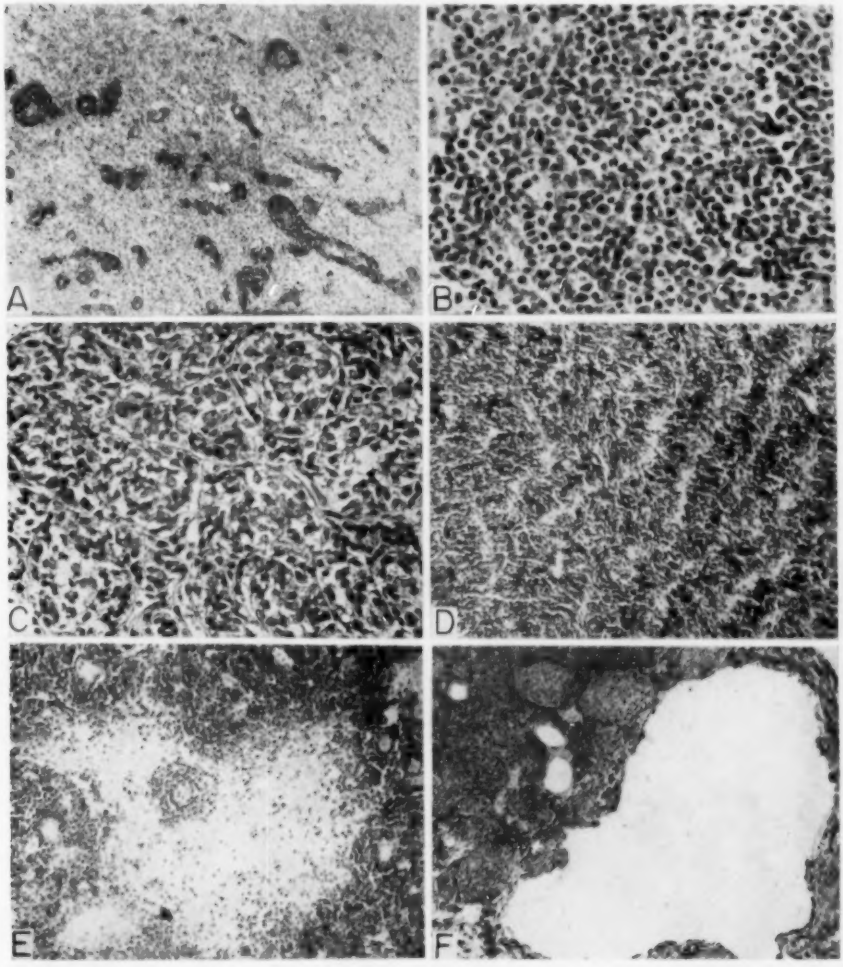

Fig. 4.—Variations in microscopic patterns in perithelial sarcomas. *A*, Case 11. Perivascular arrangement within tumor. Hematoxylin and Van Gieson; × 33. *B*, Case 10. Dense sheets of tumor cells. Hematoxylin and eosin; × 213. *C*, Case 12. Alveolar pattern. Phosphotungstic acid and hematoxylin; × 227. *D*, Case 2. Parallel cords of tumor cells separated by connective tissue. Hematoxylin and Van Gieson; × 91. *E*, Case 8. Intervascular necrosis within tumor. Hematoxylin and eosin; × 96. *F*, Case 12. Cystic degeneration within tumor (also note alveolar pattern). Phosphotungstic acid and hematoxylin; × 30.

exceptionally prominent, but in none was it the exclusive pattern. These alveolar-like structures were formed by small islands of tumor cells, surrounded by thin septa which contained capillaries and connective tissue (Fig. 4*C*, *F*). Occasionally there

was a centrally situated area of necrosis in these structures. Some type of necrosis or degeneration was common. The most frequent type was an intervascular necrosis (Fig. 4*E*), which was found to some extent in eight cases, being fairly extensive in seven of these. In this type of necrosis the tissue between the blood vessels

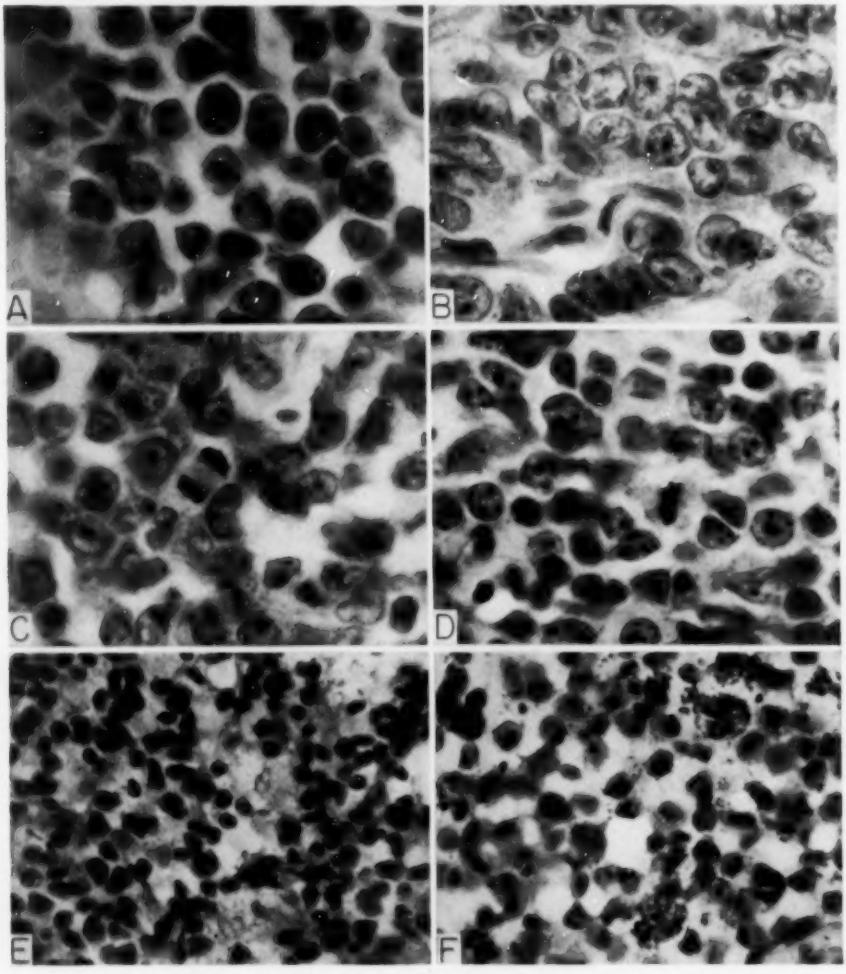

Fig. 5.—Cytological details of neoplastic cells in perithelial sarcomas. *A*, Case 8. Hematoxylin and eosin; × 813. *B*, Case 13. Hematoxylin and Van Gieson; × 813. *C*, Case 8. Note mitotic figure. Hematoxylin and eosin; × 813. *D*, Case 10. Note mitotic figure. Hematoxylin and eosin; × 813. Neoplastic cells impregnated with silver. Hortega's silver carbonate for oligodendrocytes. *E*, Case 11. × 387. *F*, Case 9. × 320.

degenerated, leaving viable the vessels and surrounding cuffs of tumor cells, consequently accentuating the picture of a perivascular arrangement. Degeneration with cyst formation (Fig. 4*F*) occurred in four cases, but in two of these there was also intervascular necrosis.

The neoplastic cells in all 13 cases were remarkably similar (Fig. 5). The nuclei were round or oval, occasionally polygonal or indented on one side, and had a vesicular appearance. They were fairly uniform in size, being about 15 μ in diameter.

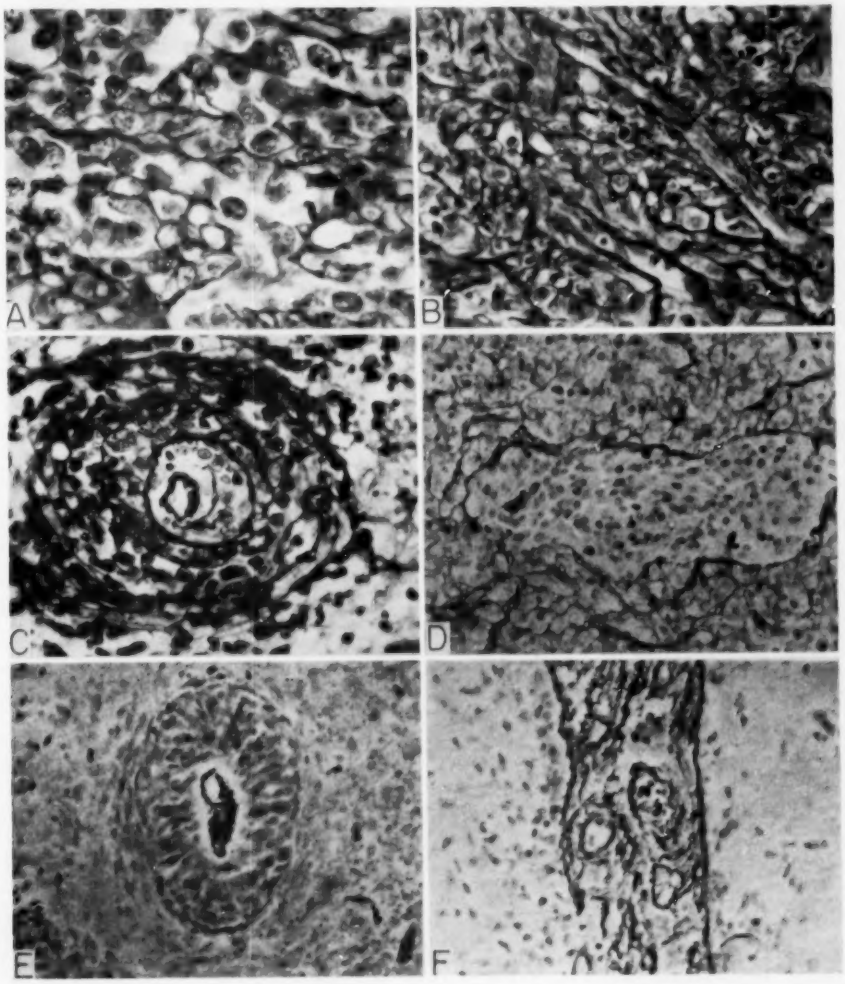

Fig. 6.—Reticulin in perithelial sarcomas. Laidlaw connective tissue stain. *A*, Case 10. Dense network surrounding individual neoplastic cells or small groups of cells. × 480. *B*, Case 10. Pericellular reticulin fibrils showing relation to capillaries. × 307. *C*, Case 8. Perivascular concentric reticulin rings. × 293. *D*, Case 13. Reticulin strands outlining alveolar pattern of tumor. × 192. *E*, Case 7. Reticulin confined to vessel wall and absent in perivascular tumor cuff. × 224. *F*, Case 7. Neoplastic invasion of leptomeninges between cerebellar folia with proliferation of reticulin fibrils diffusely and about small vessels. × 224.

Chromatin was distributed as fine particles or dust, and often there were two or three nucleoli. Cytoplasm was always scanty in amount and pale when stained with the chromatic dyes. Mitotic figures were found in all 13 tumors, but in 9 they were

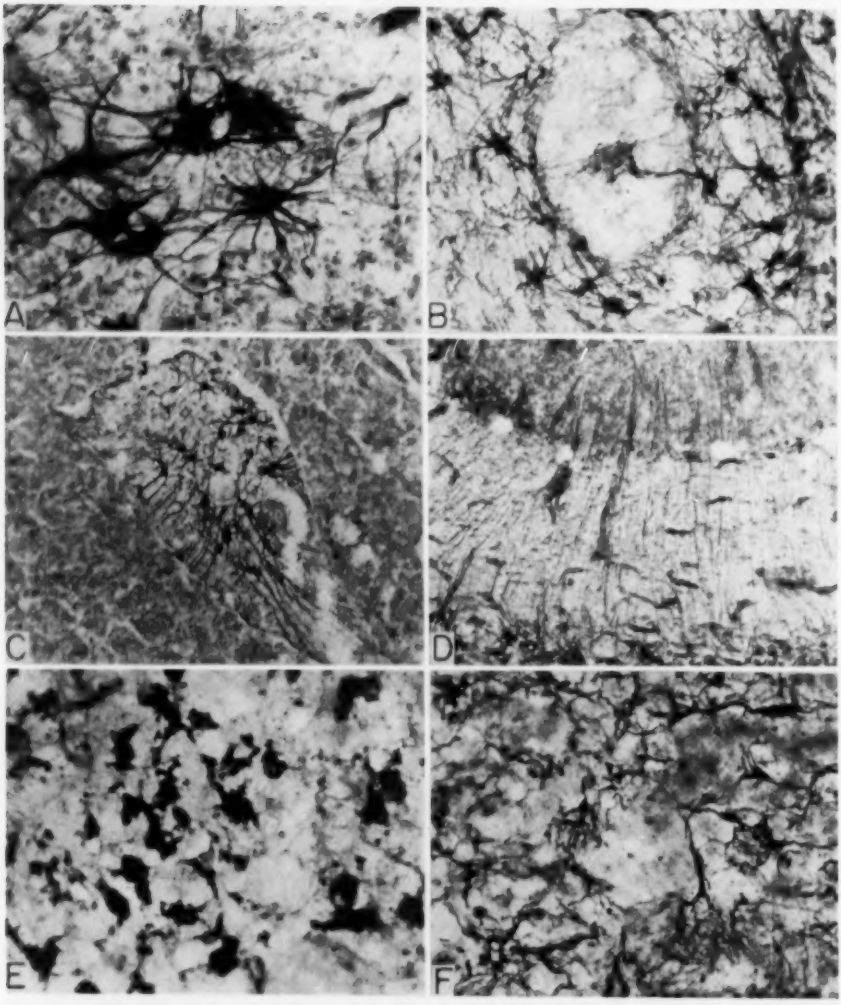

Fig. 7.—Glial elements within perithelial sarcomas. *A*, Case 10. Inclusion astrocytes within tumor. Gold chloride sublimate; × 233. *B*, Case 12. Reactive astrocytes in cerebellar white matter. Note astrocytic processes projecting through the cuff of tumor cells to the vessel wall. Gold chloride sublimate; × 227. *C*, Case 12. Island of reactive astrocytes within a nodule of neoplasm. Silver carbonate for oligodendrocytes; × 90. *D*, Case 12. Vertical gliosis extending upward through molecular layer of cerebellum. Note continuation of astrocytic processes into neoplasm which has invaded the leptomeninges. Gold chloride sublimate; × 90. *E*, Case 10. Microglial cells of ameboid type in tumor. Note how poorly the neoplastic cells in the background are outlined by the silver stain. Silver carbonate for oligodendrocytes; × 347. *F*, Case 12. Microglial cells within neoplasm which had invaded the leptomeninges. Neoplastic cells are not outlined. Silver carbonate for oligodendrocytes; × 227.

not numerous. However, in the other four cases they occurred frequently, there being two or more in each high-power field. Blood vessels were numerous in all 13 tumors, but there was no evidence of capillary or endothelial proliferation.

Reticulin fibers were found in all 13 tumors, and in 8 cases the amount was large, while in 1 case there were only a few rings around blood vessels. The distribution of this reticulin was highly variable, with some areas of the tumors containing large amounts while other areas of the same tumors contained little or none (Fig. 6). In 10 cases most of the reticulin could be related to blood vessels, there being only 3 cases in which this could not be established and leaving the possibility that the reticulin fibers were laid down by the neoplastic cells. In four cases there were significantly large areas with pericellular reticulin, but in one of these it seemed most likely that the fibers had come from blood vessel walls, and in another case a large amount of collagen was associated with the reticulin. Reticulin fibers also tended to be fairly abundant where the tumor had invaded the leptomeninges.

Ordinarily the neoplastic cells were impregnated poorly by the silver methods, but in three cases they were visualized well (Fig. 5*E, F*). However, in two of these this was not selective, because other cell types were also impregnated by the silver. In none of the 13 cases were cytoplasmic processes demonstrated on the neoplastic cells. In eight cases the silver carbonate revealed numerous macrophages (microglial cells) within the tumor or adjacent brain (Fig. 7*E, F*). Inclusion astrocytes were found in eight cases (Fig. 7). Also, in eight cases an intense reactive gliosis had occurred at the brain-tumor frontier. In three cases astrocyte processes were seen to pass through cuffs of neoplastic cells and to remain attached by footplates to now distant blood vessel walls (Fig. 7*B*).

REPORT OF CASES

CASE 1.—*History.*—A 42-year-old man complained of fatigability, irritability, occasional headaches, and episodes of mental depression for three years. Three months prior to admission he had a focal seizure involving his right hand, followed by loss of consciousness and a generalized convulsion with drawing of the face to the right side. During the three weeks before his admission he became drowsy and forgetful, vomited, and developed progressive visual failure in the left eye.

Examination.—The patient was drowsy and apathetic. His memory was impaired, and he had bilateral papilledema, with blindness of the left eye. He showed a right facial weakness, supranuclear in type.

Investigation.—Skull x-rays showed decalcification of the dorsum sellae and posterior clinoid processes. The ventriculogram showed a large left frontal expanding lesion.

Operation.—On Sept. 11, 1936, a left frontal craniotomy was performed by Dr. W. G. Penfield. The intracranial pressure was greatly increased. The tumor extended throughout the central portion of the frontal lobe and entered the middle fossa. The neoplasm was firm and seemed to consist of two separate masses.

Course.—The patient's postoperative convalescence was characterized by confusion, uncooperativeness, fecal and urinary incontinence, and complete blindness in both eyes. After a short course of x-ray therapy he was discharged from the hospital. He never improved and died six months later.

Pathology.—The tumor was reddish-brown and tough. Microscopic examination revealed a densely cellular neoplasm, which in general had an alveolar pattern, with septa composed of connective tissue and capillaries. Numerous small vessels were present, many of which were surrounded by thick cuffs of neoplastic cells. Intervascular necrosis was observed in a few areas. Adjacent cerebral tissue was invaded by perivascular spread. The neoplastic cells had

round or oval vesicular nuclei which were 14 to 16 μ in diameter and contained both fine and coarse chromatin particles, with one to three nucleoli. A thin rim of pale-staining cytoplasm was present about many of the cells. Mitotic figures were numerous. There was a rich stroma of collagenous connective tissue. The Laidlaw connective tissue stains showed in some areas many reticulin fibrils, which appeared to be derived from the capillaries and small blood vessels which were widely interspaced between small groups of neoplastic cells. In other regions, in which fewer vessels were present, large areas of neoplasm contained no reticulin. All the larger vessels had concentric reticulin rings which were expanded and separated by enmeshed tumor cells. The silver carbonate impregnations demonstrated the neoplastic cells fairly well, and mitotic figures could easily be recognized. These cells were not impregnated selectively, and endothelial cells, fibroblasts, astrocytes, and microglial cells could all be identified. The gold chloride sublimate preparation showed large numbers of inclusion astrocytes.

Case 2.—*History.*—A 9-year-old girl complained of intermittent headaches, dizzy spells, vomiting, and anorexia, all of two years' duration. Weakness in the legs had been noted for two weeks.

Examination.—The child was drowsy and dull. There were right homonymous hemianopsia and bilateral papilledema. The deep tendon reflexes were increased in the right arm, and there was a right Babinski reflex.

Investigation.—The cerebrospinal fluid contained 120 mg. per 100 cc. of protein and showed a 2+ Pandy reaction. The Lange gold curve was 0112321000. Skull x-rays showed no evidence of increased intracranial pressure but revealed an area of calcification in the left occipital lobe. A pneumoencephalogram demonstrated a large left occipital expanding lesion.

Operation.—On Aug. 18, 1939, a left occipital craniotomy was performed by Dr. W. V. Cone. The neoplasm did not present on the surface of the brain. The tumor was well demarcated from the brain by a zone of yellowish degeneration. There was no evidence of infiltration, and the gross appearance was thought to be that of a metastatic tumor. A complete left occipital lobectomy was performed, and it was believed that the tumor had been completely removed.

Course.—The postoperative convalescence was uneventful, and the patient was discharged 12 days after admission, showing slight blurring of the left optic disc, a questionable right Babinski sign, and a right homonymous hemianopsia. She was readmitted to the hospital on Jan. 19, 1940. During the previous month a small, nontender mass had appeared beneath the scalp in the left occipital region. She also had shown progressive visual impairment, anorexia, and vomiting. There was a fluctuant mass measuring 2 by 3 cm. in the left occipital region. An aspiration biopsy confirmed the diagnosis of recurrent neoplasm. She received a course of x-ray therapy and was discharged to a convalescent home. About six months after her last hospital admission she died during a series of generalized convulsions.

Pathology.—The surgical specimen was a large, irregularly shaped mass, measuring 6.5 by 4.5 by 4.0 cm. The neoplastic tissue was pink in color and firm in consistency. Microscopic examination showed a densely cellular neoplasm with a variety of architectural patterns. In some areas the cells were arranged compactly in alveolar-like structures, separated by thin fibrous connective tissue septa. In other regions the cells were arranged in long cords, many of which were parallel to one another and were separated by bands of connective tissue. Throughout the neoplasm there was a perivascular arrangement of the tumor cells, which was greatly accentuated in certain regions by an extensive intervascular necrosis. Cystic degeneration had occurred in one portion of the tumor. It was impossible to determine the type of neoplastic invasion, since the only material available for study was the tumor nodule. The neoplastic cells had uniform round to oval nuclei, about 14 to 16 μ in diameter, containing delicate chromatin particles and one or two nucleoli. Scanty, poorly stained, pale cytoplasm could be seen about some of the nuclei. Mitotic figures were infrequent. All connective tissue stains showed a rich stroma throughout the neoplasm. The Laidlaw connective tissue stains demonstrated numerous delicate reticulin fibrils scattered among the neoplastic cells, and there were frequently small groups or even single cells completely surrounded by reticulin. Most of the neoplastic cells were poorly outlined by the silver carbonate preparation, which showed scattered microglial cells.

The gold chloride sublimate impregnation showed a few poorly stained reactive astrocytes along one edge of the neoplasm, but no astrocytes were found within the central portion of the tumor.

CASE 3.—*History.*—A 35-year-old woman was brought to the hospital because of left frontotemporal headaches of two weeks' duration. For five days before admission she had noted photophobia, and on the day before admission she became confused.

Examination.—Because of confusion the patient was unable to give a history but complained of severe headaches. There was marked bilateral papilledema, and the deep tendon reflexes were hypoactive.

Investigation.—The cerebrospinal fluid, as indicated by lumbar puncture was under an increased pressure of 450 mm. of water. It appeared straw-colored and contained 16 leucocytes per cubic millimeter. The Pandy reaction was positive, and the protein content was 96 mg. per 100 cc. X-rays of the skull showed the pineal gland to be shifted 2.5 mm. to the right. An electroencephalogram indicated a large lesion in the left frontal lobe. A ventriculogram showed a moderately large expanding lesion in the inferior portion of the left frontal lobe, close to the Sylvian fissure.

Operation.—A left temporal craniotomy was performed on Feb. 20, 1940, by Dr. A. R. Elvidge, and a tumor was found at a depth of 1 cm. in the middle temporal gyrus. This tumor extended down from the Sylvian fissure and forward over the lesser wing of the sphenoid bone. It was fairly well circumscribed, grayish-white in color, and firm in consistency.

Course.—After operation the patient had complete aphasia, which never improved, and right hemiparesis, which did improve. X-ray therapy was started, and she was discharged to a convalescent home, where she died, approximately four months after operation.

Pathology.—The tumor was reddish-purple and firm and in one portion was cystic. Microscopic examination showed extensive cystic degeneration within the neoplasm, which consisted of densely packed cells arranged in sheets and around blood vessels. Many areas showed intervascular necrosis. Some sheets of tumor cells were separated into alveolar-like structures by thin septa of connective tissue. Invasion of adjacent cerebral tissue had occurred, both by direct extension and by spread along the perivascular spaces. The cells had pale, round to oval nuclei, 14 to 16 μ in diameter, and contained a delicate chromatin network with one or two nucleoli. Pale-staining but scanty cytoplasm was visible around some of the nuclei. Mitotic figures were present but were infrequent. The connective tissue stains showed a small number of delicate reticulin fibrils among some of the neoplastic cells. Reticulin was usually in relation to blood vessels or along the margins of cystic degeneration. The silver carbonate impregnations did not outline the neoplastic cells clearly but showed macrophages throughout the tumor and invaded cerebral tissue. The gold chloride sublimate impregnation showed a reactive gliosis in the adjacent brain but did not demonstrate the neoplastic cells.

CASE 4.—*History.*—A 22-year-old man complained of frontal headaches of six weeks' duration, nausea, vomiting, drowsiness of two weeks' duration, and stiffness of the neck for one week.

Examination.—He showed bilateral papilledema, a left facial weakness, diminished left abdominal reflexes, drowsiness, and weakness of the left hand, with inability to perform fine movements.

Investigation.—X-rays of the skull showed a calcified pineal gland, which was displaced posteriorly and was 2.5 mm. to the left of the midline. A ventriculogram showed evidence of a right frontoparietal expanding lesion.

Operation.—On Jan. 24, 1941, a right frontal craniotomy was performed by Dr. T. C. Erickson. The brain was found to be under increased pressure. A subcortical neoplasm was found in the frontal lobe, lying 3 to 4 cm. beneath the surface. The tumor was discrete, extremely firm, and of a homogeneous grayish-yellow color.

Course.—The patient withstood the operative procedure well but had a complete left hemiplegia with hyperactive deep tendon reflexes and ankle clonus. His postoperative course was complicated by a pulmonary atelectasis. He received a course of x-ray therapy. When discharged from the hospital, he still had a left hemiplegia and showed some mild mental changes, being somewhat facetious. He died within six months of operation, with evidence of tumor recurrence.

Pathology.—Microscopic sections showed a cellular neoplasm containing numerous capillaries and small blood vessels. Connective tissue septa and capillaries divided the cells into cords and small clusters. Some of these blood vessels were surrounded by concentric layers of neoplastic cells. Intervascular necrosis and cystic degeneration were present. In such areas, large numbers of macrophages, lymphocytes, and polymorphonuclear leucocytes were present. The neoplastic cells had relatively large vesicular nuclei which were round, oval, or polygonal and contained both fine and coarse chromatin particles. The cytoplasm was scanty, pale, and poorly stained. Mitotic figures were numerous. The pattern of invasion could not be determined, since adequate sections of surrounding brain tissue were not available for study. The Laidlaw connective tissue stains showed a rich network of reticulin fibrils, which seemed to be derived mainly from the numerous capillaries. The reticulin rings about the large vessels were expanded in a concentric fashion and were separated from one another by tumor cells.

Case 5.—*History.*—A 43-year-old man had progressive impairment of memory for three years. For six months he had gradually increasing deafness, and for two months, unsteadiness of gait. Two months before admission he became unable to move his left arm and leg and complained of numbness of the left foot. Right frontal headaches occurred intermittently for one month, and he had some nausea and vomiting.

Examination.—He was apathetic and disoriented and had a left hemiparesis. The deep tendon jerks on the left were hyperactive, with a left Babinski sign and absent cremasteric and abdominal reflexes on the same side. Pain, light touch, vibratory, and position sense were diminished on the left. He had bilateral papilledema. The pupils were small and slightly irregular and reacted sluggishly to light. Auditory acuity was decreased bilaterally, and the gag reflex was absent. The 11th and 12th cranial nerves were paretic on the left side.

Investigation.—A ventriculogram showed an expanding lesion in the right frontoparietal region near the midline.

Operation.—On Sept. 14, 1943, a right parietal craniotomy was performed by Dr. A. R. Elvidge. The postcentral convolution was widened. About 1.0 to 1.5 cm. below the surface a tumor was found. This consisted of a firm, pink, well-demarcated nodule about 3 cm. in diameter, which was removed.

Course.—After operation the patient had a persistent paralysis of the left side, and the sensory loss remained the same. The papilledema subsided, and he became alert and oriented. He was given x-ray therapy and was discharged to a convalescent home, where his condition deteriorated, and he died approximately five months after operation.

Pathology.—Microscopic examination showed a relatively cellular neoplasm with a prominent perivascular arrangement. Intervascular necrosis was present in some areas. The adjacent cerebral tissue was diffusely involved, both by direct extension and by spread along the perivascular spaces. The neoplastic cells were 14 to 16 μ in diameter and had round, oval, or polygonal nuclei, usually containing two to three nucleoli. The cytoplasm, when visible, appeared as a scanty, poorly stained, pale, homogeneous structure. Mitotic figures were infrequent. Numerous macrophages were scattered throughout areas of partial necrosis. Connective tissue stains showed reticulin fibrils only in relation to blood vessels. The perivascular reticulin rings were separated by enmeshed neoplastic cells. There was practically no collagenous connective tissue ingrowth in the areas undergoing necrosis. The silver carbonate preparation showed large numbers of compound granular corpuscles and active adult microglial cells, but the neoplastic cells were poorly outlined and showed no processes. The gold chloride sublimate preparation showed a reactive gliosis in the involved cerebral tissue, with occasional inclusion astrocytes within the neoplasm.

Case 6.—*History.*—A 24-year-old woman had blurring of vision for two and a half years. Fourteen months prior to admission she became pregnant and had daily headaches, nausea, and vomiting, all of which persisted after delivery. With the headaches she had diplopia. For five months before admission she had generalized weakness, loss of weight, and increasing irritability.

Examination.—Examination revealed bilateral papilledema, diplopia, nystagmus on right lateral gaze, hyperactive deep tendon reflexes, and staggering gait with a tendency to fall to the right side.

Investigation.—A ventriculogram showed enlargement of the entire ventricular system, with suggestive evidence of an expanding lesion in the region of the foramen magnum.

Operation.—On Jan. 9, 1945, a suboccipital craniectomy was performed by Dr. W. V. Cone. Between the dura and the vermis of the cerebellum, there was a soft reddish film of tissue. A diffuse tumor was found in the left cerebellar hemisphere and the roof of the fourth ventricle.

Course.—The patient withstood the operative procedure well and except for a prolonged period of temperature elevation her postoperative course was uneventful. A course of x-ray treatment was given over the posterior fossa. When discharged from the hospital, she was ambulatory, free of headaches, and mentally alert. There was still slight unsteadiness of gait. She died 21 months postoperatively. During the last few months of her life she was blind, was confined to bed, and suffered from intermittent headaches.

Pathology.—Microscopic examination showed cerebellar tissue with extensive invasion of the leptomeninges by a densely cellular neoplasm. There was marked invasion of all layers of the cerebellum along perivascular spaces. In one area the granular cell layer was almost completely replaced by closely packed perivascular cuffs of neoplasm. The cells had large oval to round nuclei, containing a fine chromatin network, with one or two nucleoli. In some areas the nuclei were more elongated and slightly curved, with a definite tendency toward streaming. The cytoplasm was scanty and poorly stained. Mitotic figures were present but were not numerous. The Laidlaw connective tissue stain showed reticulin fibrils usually only in relation to blood vessels. The perivascular rings were separated by enmeshed tumor cells. Within the invaded leptomeninges reticulin fibrils were seen among the neoplastic cells independent of blood vessels. Metallic preparations were not available for study.

Case 7.—*History.*—A 26-year-old woman entered the hospital, complaining of unsteadiness of gait for one and one-half years, blurred vision for five months, thick speech for several months, occipital headaches and vomiting for three weeks, and impaired hearing in the left ear for an unknown length of time.

Examination.—She had bilateral papilledema, paresis of the left fourth cranial nerve, slightly diminished auditory acuity on the left, dysarthria, dysmetria, ataxia of all extremities which was more marked on the left side, a hypoactive left knee jerk, and nystagmus.

Investigation.—A ventriculogram showed evidence of an expanding lesion in the superior aspect of the left cerebellar hemisphere.

Operation.—On Oct. 18, 1949, a suboccipital craniectomy was performed by Dr. A. R. Elvidge. An invasive neoplasm was found within the superior portion of the left cerebellar hemisphere, and at no point was there clear demarcation of tumor from normal brain.

Course.—The patient withstood the operative procedure well, and her postoperative convalescence was uneventful. She received a course of x-ray therapy. The papilledema receded, her speech improved, and she had no headache. The only residual symptom was slight ataxia. She has continued to do well, and when last heard from, four years following the operation, she was asymptomatic and caring for her family.

Pathology.—For the most part it was impossible to distinguish normal cerebellum from the tumor, but in some areas over the folia and within the invaded white substance the tissue had a glistening grayish-white appearance and represented neoplasm. Microscopic examination showed diffuse infiltration of the cerebellum by a densely cellular neoplasm, which had invaded principally along the perivascular and subarachnoid spaces. Thick cuffs of tumor cells surrounded blood vessels throughout all the layers of the cerebellum. There was no single neoplastic nodule but only varying degrees of infiltrating neoplasm within the cerebellum. The cells had relatively large, oval to round nuclei, some of which were indented on one side. There was a fine chromatin network with one or two nucleoli. Only a small rim of poorly stained cytoplasm could be seen. Mitotic figures were present but were not numerous. The Laidlaw connective tissue stains showed reticulin fibrils among the tumor cells only where invasion of the leptomeninges had occurred. Throughout the neoplasm, within the cerebellum, reticulin was found only in relation to vessels. Silver carbonate preparations did not outline the neoplastic cells but showed large numbers of active microglial cells. The gold chloride sublimate impregnations showed a marked gliosis within the molecular layer of the cerebellum and large numbers of reactive astrocytes within the cerebellar white matter. Astrocytic processes frequently could be seen passing through the perivascular neoplasm to end in footplates on the blood vessel wall.

CASE 8.—*History.*—A 53-year-old man was referred to this hospital on May 24, 1950, with the presumptive diagnosis of right cerebral neoplasm. He had sustained a head injury in 1917. A slowly progressive left hemiplegia had been noticed during the nine years prior to admission. He had been studied on several occasions in a Veterans Administration Hospital. Pneumoencephalograms performed in March, 1948, March, 1950, and November, 1951, all showed enlargement of both lateral ventricles, with the right being larger than the left and with the septum pellucidum shifted 2 mm. to the right side. He began to have left-sided seizures in August, 1949, which continued at infrequent intervals. An electroencephalogram showed a right frontotemporal abnormality. For two years prior to admission he had had episodes of confused behavior. Several weeks prior to admission to this hospital, right-sided carotid arteriography was done, after which the patient became completely paralyzed on the left side. He gradually became confused and finally stuporous.

Examination.—Examination at the time of admission here revealed a confused and stuporous patient with a complete left hemiplegia. Papilledema was present on the right side. The right pupil was larger than the left, although both reacted to light. Position sense and two-point discrimination were lost on the left side. The deep tendon reflexes were hyperactive on the left, and there were bilateral Babinski signs.

Investigation.—Skull x-rays showed the pineal gland to be shifted 3 mm. to the left, whereas before it had been shifted slightly to the right.

Operation.—A right parietal craniotomy was performed on June 8, 1950, by Dr. A. R. Elvidge. The convolutions were flattened and had a whitish discoloration. A deep right parietal neoplasm was found about 3 cm. beneath the cortex, which extended almost to the midline. The tumor was firm in consistency and finely lobulated. It was whitish-gray in color and could easily be dissected away from the surrounding brain.

Course.—Postoperatively the patient regained consciousness but never improved over his preoperative condition. Within two weeks his condition began to deteriorate, and he died one month after operation. An autopsy was performed.

Pathology (Autopsy and Surgical Specimen).—A complete postmortem examination showed no significant abnormalities outside of the central nervous system. The postoperative defect, deep within the right frontoparietal region, was surrounded by a narrow zone of hemorrhagic softening. There was marked distortion of the ventricular system, and a subtentorial pressure cone was present on the right side. After the brain was sectioned, a tumor was found which involved the centrum of the right hemisphere. It invaded the corpus callosum and followed the white substance of the convolutions up to the gray matter. The basal ganglia and thalamus were not involved. Microscopic sections showed a densely cellular neoplasm, with broad sheets of cells which frequently were arranged as cuffs about blood vessels. There was a moderate amount of intervascular necrosis. Adjacent cerebral tissue was diffusely invaded by direct extension of the neoplastic cells and by spread along the perivascular spaces. Small blood vessels surrounded by cuffs of neoplasm were seen over 1 cm. from the tumor boundary, well within otherwise normal cerebral tissue. The cells were uniform, having a relatively large oval or round nucleus with a delicate chromatin network. The cytoplasm was scanty and poorly stained. Mitotic figures were extremely numerous. Connective tissue stains showed a relatively small amount of collagenous connective tissue within the neoplasm. The Laidlaw connective tissue stains showed a sparse distribution of reticulin, which was mainly related to the blood vessels or to areas of necrosis where connective tissue replacement had occurred. Perivascular reticulin rings were usually separated and enlarged by neoplastic cells. A silver carbonate preparation showed large numbers of microglial cells of the active ameboid type and numerous compound granular corpuscles. The neoplastic cells were not stained by this method. The gold chloride sublimate impregnations showed a reactive gliosis in the adjacent cerebral tissue and frequent inclusion astrocytes within the tumor.

CASE 9.—*History.*—For three years before admission a 16-year-old girl had been having momentary episodes of automatism, preceded by a strange body sensation. Occasionally with these episodes she would vomit. During the year before admission the spells increased in frequency. About a month before admission she began to have severe generalized headaches.

Examination.—On admission she was mentally dull and had bilateral papilledema.

Investigation.—By x-ray the skull was slightly asymmetrical, the right side being larger than the left. Ventriculography indicated an expanding lesion in the right temporal lobe.

Operation.—On Nov. 2, 1950, a right temporoparietal craniotomy was performed by Dr. A. R. Elvidge, and a large tumor was found in the anterior temporal lobe, 2 or 3 cm. below the surface of the cortex. It consisted of a large necrotic mass, the center of which was yellowish, granular, and necrotic, but in addition to this tissue there were areas of tough tumor tissue.

Course.—For some time after operation she had headaches and her intracranial pressure was high. She was discharged to another hospital, where, in spite of x-ray therapy, her course was progressively downward, and she died approximately five months after operation.

Pathology.—Microscopic examination disclosed a very cellular neoplasm. The cells were arranged in sheets, with occasional small incomplete alveolar-like structures, separated by fibrous tissue septa and capillaries. A prominent perivascular pattern was present at the border of the tumor. Neoplastic invasion was almost entirely by way of the perivascular spaces. Cuffs of tumor cells about blood vessels were seen occasionally within cerebral tissue at a considerable distance from the main neoplasm. The cells had round to oval nuclei, which were occasionally indented on one side and contained fine chromatin particles, with one to three nucleoli. There was a thin rim of poorly stained cytoplasm. Mitotic figures were present but were not frequent. The Laidlaw connective tissue stain showed delicate reticulin fibrils, usually only in relation to blood vessels. The perivascular reticulin rings were separated and expanded by enmeshed neoplastic cells. The only area in which numerous reticulin fibrils were shown independently of blood vessels, and apparently in close relationship with the tumor cells, also showed a large amount of collagenous connective tissue. Silver carbonate preparations outlined the neoplastic cells relatively well and showed more abundant cytoplasm than was seen on the chromatic sections. No cytoplasmic processes were demonstrated. Numerous macrophages filled with brown pigment were present, together with ameboid forms of adult microglial cells. The gold chloride sublimate preparations showed a marked reactive gliosis in the involved cerebral tissue. Astrocytic processes were dense about the perivascular collections of neoplasm and appeared to have been pushed aside. Occasionally an astrocyte process could be followed through the neoplastic cells to the vessel wall. Numerous inclusion astrocytes were present in the neoplasm itself.

CASE 10.—*History.*—A 63-year-old man entered the hospital, complaining of headaches, confusion, and weakness on the left side. For two years he had had headaches which had increased in severity during the three months before admission. For about four months he had complained of rapid fatigability and unsteady gait. Two weeks before admission he had become weak on the left side, and one week before admission he suddenly became comatose for a short time. This was followed by persistent confusion.

Examination.—On examination he had a bilateral external ophthalmoplegia, worse on the left than on the right side. He had a left hemiparesis, with increased deep tendon reflexes on the same side.

Investigation.—There was an albuminuria. The cerebrospinal fluid protein was elevated to 120 mg. per 100 cc. An electroencephalogram showed generalized damage in the right centrotemporal region. The pineal body was shifted 8 mm. to the left of the midline and displaced downward and backward. A ventriculogram demonstrated a right posterior temporal expanding lesion.

Operation.—A right temporoparietal craniotomy was performed on March 16, 1951, by Dr. A. R. Elvidge. The posterior temporal region was softened. A tumor was found here which was gray in color and firm in consistency, being adherent to the middle cerebral vessels and to the meninges. The tumor filled the upper and lateral two-thirds of the right temporal lobe, and a mass 2 to 3 in. in diameter was enucleated.

Course.—The patient recovered slowly from the operative procedure and frequently had episodes during which he would not respond. By the 11th postoperative day he could talk and move his left arm. He did fairly well for several months; then his general condition began to deteriorate, and he died from a recurrence of the neoplasm 18 months after operation.

Pathology.—Microscopic examination showed a densely cellular neoplasm, arranged for the most part as broad sheets of cells with many areas showing a prominent perivascular arrangement. There was no alveolar pattern, and very little collagenous connective tissue could be

found within the neoplasm. Cystic degeneration was not observed, but there were a few areas of intervascular necrosis. The neoplasm had involved adjacent cerebral tissue by direct extension as well as along the perivascular and subarachnoid spaces. The neoplastic cells had large oval to round vesicular nuclei, containing delicate particles of chromatin with one or two nucleoli. The cytoplasm was scanty and poorly stained. Mitotic figures were frequently observed. The Laidlaw connective tissue stains showed a rich network of delicate reticulin fibrils throughout a large part of the tumor. In many areas individual neoplastic cells or small groups of cells were surrounded by reticulin fibrils. The sections impregnated by the silver carbonate method showed large numbers of active adult microglial cells throughout the tumor. The neoplastic cells were visible indistinctly in the background and were not impregnated well by this method. Scharlach-R fat stains showed very little neutral fat within macrophages. The gold chloride sublimate impregnation revealed a reactive gliosis in adjacent cerebral tissue, as well as inclusion astrocytes in the neoplasm.

Case 11.—*History.*—A 59-year-old man was admitted to the hospital, complaining of headaches and loss of appetite for two months and episodes of vomiting for one month. For three months he had been slightly drowsy and over the same time had complained of loss of hearing.

Examination.—On examination he had bilateral papilledema and a lower left homonymous quadrantal visual field defect.

Investigation.—The cerebrospinal fluid protein was 124 mg. per 100 cc., with a positive Pandy reaction. From a ventriculogram it was believed that there was one or possibly two expanding lesions in the right parietotemporal region. An electroencephalogram showed minimal slowing of activity in the right posterior temporoparietal region.

Operation.—The patient was operated upon by Dr. W. G. Penfield on June 26, 1951, and a large tumor was found in the right anterior occipital and posterior parietal and temporal lobes. This neoplasm was yellowish-red in color and tough in consistency but had no clear demarcation from the surrounding brain. It was attached to the dura and was quite vascular. There was extension into the right hemisphere for a distance of 6 to 7 cm., reaching, but not entering, the right lateral ventricle.

Course.—After operation he had a left hemiparesis, which gradually improved, and a left homonymous hemianopsia, which did not change. Except for a few focal motor seizures he did well. He was given a course of x-ray therapy, after which he gradually developed signs of increased intracranial pressure and died five months after operation.

Pathology.—Microscopic examination revealed a cellular neoplasm which in many regions was sharply demarcated from surrounding cerebral tissue but in others showed invasion along the subarachnoid and perivascular spaces. There were large numbers of small blood vessels throughout the tumor, with obvious perivascular cellular arrangement. An alveolar-like pattern was present in several areas, with thin septa of connective tissues surrounding groups of neoplastic cells. Infrequent small areas of cystic degeneration were found. The neoplastic cells had relatively large, round to oval nuclei, containing numerous delicate particles of chromatin and one or two nucleoli. Only a scanty rim of cytoplasm was present, and it stained poorly. Mitotic figures were present but were not numerous. A large amount of collagenous connective tissue was present throughout some portions of the neoplasm, while other areas showed none. Reticulin fibrils were present throughout most of the neoplasm, being most conspicuous in those areas containing collagen. Many reticulin fibrils, however, did not appear to be related to blood vessels or strands of collagenous connective tissues. Concentric rings of reticulin were present about the blood vessels in the main neoplasm and in the invaded cerebral tissue. Sections impregnated by the silver carbonate method showed some of the neoplastic cells relatively well, while large numbers were not outlined at all. In general, cellular outlines were clearer in those regions of the tumor containing connective tissue, and in all probability many of these cells were fibroblasts. However, some areas of what appeared to be pure neoplasm and most of the perivascular cuffs of tumor cells in the invaded cerebral tissue contained cells, the nuclei of which were clearly demonstrated by the silver technique. Cytoplasmic processes were not seen in these cells. Numerous adult microglial cells and compound granular corpuscles were scattered throughout the tumor. The gold chloride sublimate preparations showed active gliosis in adjacent and invaded cerebral tissue, with scattered degenerative astrocytes throughout the neoplasm.

CASE 12.—*History.*—A 22-year-old woman was well until four months prior to admission, when she developed increasingly severe generalized headaches. During the two weeks preceding her entry she had had a constant headache with nausea and vomiting. The pain in her head radiated into the posterior cervical region. For one week she had noted dizziness and an unsteady gait. Between 1946 and 1949 she was treated for tuberculosis of the lumbar spine and had recovered.

Examination.—Examination revealed questionable papilledema of the right optic disc. She had severe headache and could not sit up because of vertigo. She was conscious and alert.

Investigation.—X-rays of the lumbosacral spine showed partial destruction of the fourth lumbar vertebra and of a partly sacralized fifth lumbar vertebra. There was evidence that these two vertebrae had fused but no suggestion of active bone disease. A ventriculogram disclosed evidence of a left cerebellar tumor.

Operation.—Operation was performed on Nov. 27, 1952, by Dr. A. R. Elvidge. A neoplasm was visible on the anterior and lateral surfaces of the left cerebellar hemisphere. The lateral one-third of the cerebellar hemisphere was amputated. An additional nodule of neoplasm was found and removed from the upper pole of the left cerebellar hemisphere.

Course.—The postoperative convalescence was uneventful. At the time of discharge from the hospital she showed slight blurring of the optic discs, right facial hypesthesia, left facial weakness, nystagmus on gaze to the left, and incoordination of the left extremities. X-ray therapy was to be carried out at another hospital. Thirteen months after operation this patient was asymptomatic and regularly employed.

Pathology.—Microscopic examination of the solid nodule revealed a densely cellular neoplasm. The cells were arranged in an alveolar-like pattern and separated by thin strands of connective tissue. Several areas of cystic degeneration were present throughout the tumor. The neoplastic cells had large round or oval vesicular nuclei, containing numerous chromatin particles and one or two nucleoli. The cytoplasm was clear, poorly stained, and scanty. The nuclei were about 14 to 16 μ in diameter. Mitotic figures were present but were not numerous. There was no clear perivascular arrangement of the cells. However, many of the smaller arterioles and capillaries contained the same type of large cells in or on their walls. Occasionally, such cells were seen within the lumina of the blood vessels. The Laidlaw connective tissue stains showed fine strands of reticulin, which for the most part were about blood vessels or within the thin septa forming the alveolar-like structures of the tumor. In some areas of the tumor, however, especially near the periphery, there was a more abundant distribution of reticulin fibrils interspersed between the neoplastic cells. The gold chloride sublimate and silver carbonate preparations showed a few small islands of reactive astrocytes. Active microglial cells and compound granular corpuscles were occasionally seen, especially in the areas of cystic degeneration. The neoplastic cells were not impregnated by either of the metallic methods used. Chromatic sections of the excised cerebellar tissues showed extensive perivascular and leptomeningeal spread of the neoplasm. The neoplastic cells arranged about the blood vessels were seen to lie outside the vascular reticulin and were seldom seen in a meshwork of reticulin fibrils. The gold chloride sublimate preparations showed a marked increase of large reactive astrocytes throughout the cerebellar white matter and granular cell layer, and a striking vertical gliosis of the molecular layer. Astrocytic processes were visible passing through the perivascular neoplastic cells, often with the footplate still attached to the vessel wall. Similarly, where the neoplasm had invaded the leptomeninges, areas were frequently seen where astrocytic processes passed from the molecular layer of the cerebellum across the region occupied by the tumor. This suggested that the neoplasm had invaded beneath the pia-glial membrane and lengthened the astrocytic processes involved in the vertical gliosis. The silver carbonate preparation showed numerous microglial cells in the areas of involved cerebellum, as well as a marked proliferation of microglia within the neoplasm which had involved the leptomeninges. The neoplastic cells were not outlined by these metallic methods.

CASE 13.—*History.*—A 29-year-old man had increasingly severe bifrontal headaches for five months. More recently the pain had also been felt across the occipital region, with spread into the neck. During the month prior to admission he had noticed dizziness on rapid change in posture and had experienced increasing difficulty in walking. Nausea, vomiting, diplopia, and stiff neck were present for one week before hospital admission.

Examination.—Examination disclosed severe bilateral papilledema and retinal hemorrhages. Nystagmus was present on gaze to either side and vertically. The head was held tilted to the left. There was marked incoordination of the left upper extremity, and the patient had an ataxic gait.

Investigation.—X-rays of the skull showed complete decalcification of the dorsum sellae. A ventriculogram suggested a left cerebellar expanding lesion.

Operation.—Operation was performed on Sept. 19, 1953, by Dr. W. V. Cone. Slight widening of the cerebellar folia on the left and downward displacement of the cerebellar tonsils were the only abnormalities noted when the dura was opened. The neoplasm was found within the left cerebellar hemisphere, about 1 cm. beneath the surface. This was a grayish-white, soft tumor which was invasive and appeared grossly to be a glioma. On the ventrolateral surface of the left cerebellar hemisphere the neoplasm had broken through the pia and was attached over a 0.5 cm. area to the dura covering the lateral sinus. All gross neoplasm was removed, together with most of the left cerebellar hemisphere.

Course.—The patient recovered from the operation satisfactorily, and when discharged from the hospital he was ambulatory and free of headaches. His papilledema had almost cleared and he showed only mild left cerebellar signs. He was started on a course of x-ray therapy, which he was to complete as an outpatient. Since discharge from the hospital he has remained well during the three months that have elapsed since operation.

Pathology.—Microscopic sections revealed a densely cellular neoplasm with a variable pattern. The larger portion of the tumor consisted of thick cords or sheets of densely packed cells separated by strands of connective tissue. In other areas of the neoplasm the cells were more loosely arranged and showed a definite perivascular pattern. Very little necrosis was seen. Cerebellar tissue was invaded both directly and by spread along the leptomeninges. Little collagenous connective tissue was present. In the densely cellular portions of the tumor reticulin fibrils were found associated with normal-appearing blood vessels. It did not appear as though the neoplastic cells were intimately related to strands of reticulin. In the more loosely arranged portions of the tumor, containing perivascular cuffs, reticulin fibrils could not be stained. The neoplastic cells in both the dense and the loosely arranged portions of the tumor appeared the same under high magnification. The nuclei were 14 to 16 μ in diameter and were round to oval, often with an indentation on one side. Scattered throughout the nuclei were delicate chromatin particles with one or two nucleoli. There was a thin border of lightly stained cytoplasm. Mitotic figures were present but were not numerous. Only small portions of the neoplasm were available for metallic techniques, and in these the neoplastic cells were not clearly seen in either the gold chloride sublimate or the silver carbonate preparation.

COMMENT

We believe that these 13 cases are similar enough, both clinically and pathologically, to be considered profitably as one group and that they represent the commonest form of primary intracranial sarcoma. It would seem that this is the same type of tumor as those described by Bailey,[1] Hsü,[11] and others [14] as perithelial and alveolar sarcomas; by Abbott and Kernohan [12] as perivascular sarcomas; by Yuile [18] and Kinney and Adams [17] as reticulum cell sarcomas, and by Russell and co-workers [20] as microgliomas or microglioblastomas.

If this is true, certain generalities can be stated regarding the clinical and pathological aspects of these cases. The tumor may occur at any age from the first to the eighth decade but is commonest in the young or middle-aged adult. There may be a preponderance among males, but either sex may be involved. There is no characteristic location of the neoplasm within the brain, and therefore no typical clinical syndrome exists. Most cases complain of headache and vomiting and show evidence of increased intracranial pressure. If the neoplasms are discrete, as they were to a varying degree in the present series, localization can usually be accurately

made by ventriculography. One cannot by laboratory methods or specialized diagnostic techniques establish the diagnosis of perithelial sarcoma preoperatively. These are rapidly growing malignant neoplasms of the brain with duration of symptoms usually varying from weeks to months. If untreated when they first seek medical aid, these patients commonly survive only a few days to a few months. Usually operation offers only temporary relief from increased intracranial pressure, and if the patient survives surgical intervention death usually occurs within six months. The value of x-ray therapy remains doubtful, although most recommend its use. Our Case 7, who has survived four years without evidence to date of recurrence, makes us feel that x-ray therapy was probably beneficial, since it was suspected at operation that all of the neoplasm had not been removed. Case 12 also had x-ray therapy, and, while only 13 months has elapsed since operation, she is completely asymptomatic and regularly employed. It is cases of this type that make us feel that surgical excision and postoperative x-ray therapy should be carried out in each case when feasible.

These neoplasms vary from discrete masses with a pseudocapsule of degenerated cerebral tissue to diffuse spread within relatively large areas of the brain, involvement often being macroscopically invisible. They are usually deep but may extend to the surface and locally involve the overlying meninges or grow into the lateral or fourth ventricle. The division of these neoplasms into four different subtypes, as suggested by Abbott and Kernohan,[12] may be of value but did not aid us in the interpretation of our material. The tumor may be soft or firm in consistency, varying in color as white, gray, yellow, or pink, and with or without cystic or hemorrhagic degeneration. There is usually only one cerebral neoplasm; rarely multiple tumors are present. In a few cases in which complete autopsies have been done, similar extracranial lesions have been found. It is not clear whether these represent independent coexisting neoplasms, as suggested by Russell and associates,[20] or whether they are primary or metastatic lesions in relation to the intracranial tumor.

The microscopic appearance of these neoplasms is fairly uniform. All are densely cellular, with varying numbers of mitotic figures. Some perivascular cellular arrangement is almost invariably seen within the neoplasm, often accentuated by intervascular necrosis, and perivascular spread of the neoplasm in adjacent cerebral tissue is constant. Occasionally in a discrete nodule one sees predominantly an alveolar or "pseudoalveolar" pattern, or an arrangement of cords of cells separated by strands of connective tissue. All would agree that there are varying amounts of increased reticulin fibrils associated with these tumors, but there is no unanimous opinion concerning the origin and significance of this connective tissue. Some ‖ have felt that the reticulin was produced by the neoplastic cells, while others ¶ have suggested that it was fibroblastic in origin. We feel that there is some evidence to support the latter suggestion, in that we observed reticulin to be present most constantly in relation to vessels, either as concentric rings or as diffusely spreading fibrils, and to areas of leptomeningeal invasion, where, as with other types of tumor invasion, a connective tissue proliferation is often seen. Within deeper areas of solid tumor, in regions containing relatively few blood vessels, there were often wide zones of neoplastic cells in which no reticulin fibrils could be found. On the other hand, in

‖ References 1 and 12.
¶ References 7 and 17.

those regions in which varying degrees of collagenous connective tissue were present, forming the stroma of the neoplasm, associated reticulin fibrils were always demonstrated. It would therefore seem that, while reticulin is always present in these tumors, it may vary considerably in amount and is not always as extensive as in the two cases described by Kinney and Adams.[17] The reticulin certainly is not produced by all the neoplastic cells and, if it is at all, may vary with maturity of the cell and the rate of neoplastic growth. The neoplastic cells in all our cases appeared the same and closely resembled those described and illustrated by others in this type of neoplasm. Microglial cells in various forms and stages of phagocytosis were present in all our tumors. While Hortega's silver carbonate stain for oligodendroglia was used in our material, and not the variant for microglia, these latter cells were always stained quite satisfactorily when present. The tumor cells were well outlined in three of the cases by this metallic technique but appeared essentially the same as when stained by the usual chromatic methods. It was always possible to distinguish between the neoplastic cells and the various forms of microglial cells, and on the

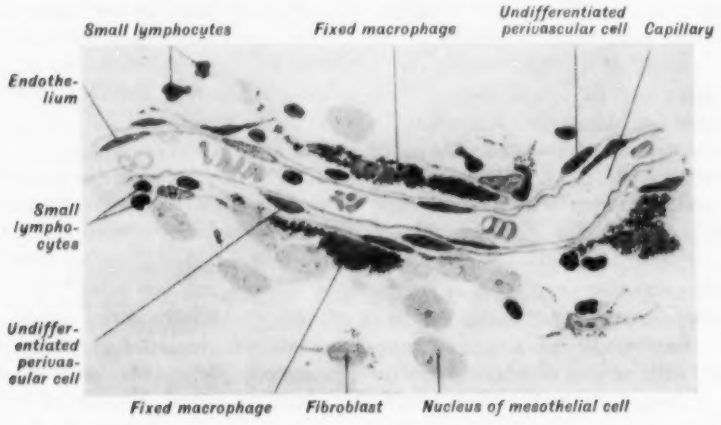

Fig. 8.—(After Maximow.) Stretch preparation of omentum of a rabbit vitally stained with lithium carmine, showing a capillary with undifferentiated perivascular cells. Hematoxylin stain; × 500. (Permission W. B. Saunders Company.)

basis of our silver preparations we did not feel the tumors were of microglial origin. With use of metallic stains, reactive and degenerating astrocytes could be shown within portions of these neoplasms, and the manner in which the tumor cells extend into the surrounding brain, isolating and finally destroying islands of parenchymal tissue, could be demonstrated. The perivascular tumor cells surrounding capillaries were bridged by elongated astrocytic processes still attached to the vessel wall.

The various names given to this type of neoplasm either have been descriptive (perivascular or alveolar) or have represented an attempt by the particular author to signify the source (leptomeningeal or perithelial) or the type-cell (reticulum cell sarcoma, reticuloendothelioma, or microglioblastoma) of the tumor. Most neuropathologists would agree that these neoplasms are sarcomas arising from either the leptomeningeal or the perivascular connective tissue of the brain. Modern histologists [21] recognize in the adult organism an undifferentiated mesenchymal perivascular

cell arranged along the blood vessels and, especially, the capillaries (Fig. 8). This cell resembles, but is slightly smaller than, the fibroblast. Numerous observations have shown that these are not ordinary fibroblasts but undifferentiated cells which, under the influence of various stimuli (tissue culture, inflammation, injection of blood toxins), may develop into new cell types. They are considered by many as having much the same properties as the primitive reticular cells of the blood-forming tissues and of the free lymphoid stem cells, and thus are probably the precursor of the fixed perivascular macrophage. The perivascular undifferentiated cells can be readily distinguished from the fixed macrophage (histiocyte) which lies in or just outside the vessel wall, by methods of vital staining, since the undifferentiated cells have no phagocytic properties.

These undifferentiated cells or the perivascular (or leptomeningeal) macrophages would seem to be the most likely cells of origin of this type of neoplasm. If one considers the undifferentiated perivascular cell as the neoplastic source and feels that this cell is identical with the primitive reticular (reticulum) cell of hematopoietic tissues, then the term reticulum cell sarcoma is logical and perhaps should be adopted. While the primitive reticular and perivascular cells are similar, we do not feel it has been proved they are identical. This fact, together with the unavoidable connotation that the reticulin fibrils are produced by the neoplastic cells of a reticulum cell sarcoma, which may or may not be true, has made us feel that at present another term is desirable.

If one accepts the perivascular or leptomeningeal macrophage as the cell of origin in the neoplasm, the term reticuloendothelioma has some justification. Similarly, if one considers the fixed macrophages as a source of neoplastic microglia, the term microglioblastoma must be considered. We are not convinced, however, that this neoplasm represents anaplastic or dedifferentiated microglia originally present within the brain or arising from perivascular macrophages.

We have preferred to think of the perithelium [22] as the connective tissue fibers (collagen and/or reticulin) and cells (fibroblasts, macrophages, undifferentiated mesenchymal cells) which surround the cerebral blood vessels and extend beyond the limits of the invaginated piarachnoid sheaths along the capillary walls, and we feel that this term may still be useful in pathology, if not in histology. We suspect that these neoplasms originate from an undifferentiated mesenchymal perivascular cell. The term perithelial sarcoma is well established, was suggested by Bailey, who first attempted to clarify this subject, and indicates the probable site of origin as well as the most characteristic pathological feature of this group of tumors.

SUMMARY

1. Perithelial sarcoma usually occurs in young or middle-aged adults and may involve either sex.

2. Perithelial sarcoma is a rapidly growing malignant neoplasm which may involve any portion of the brain and produces no characteristic clinical syndrome.

3. Most of the patients in this series complained of headache and vomiting and had papilledema when examined.

4. All of the tumors in this series were accurately localized by encephalography or ventriculography, which were the most important diagnostic procedures.

5. Although most cases were benefited only temporarily, if at all, by surgical and x-ray therapy, the satisfactory survival to date of two patients for 48 months and 13 months, respectively, makes us feel that surgical excision, when feasible, followed by x-ray therapy is the treatment of choice.

6. While only one case had a complete autopsy, it was felt clinically that each patient had a single primary intracranial neoplasm which was fairly discrete but showed varying degrees of diffuse perivascular spread into the adjacent neural parenchyma.

7. The neoplastic cell appeared the same in all cases, with a round or oval vesicular nucleus about 16 μ in diameter and usually containing two or three nucleoli. The cytoplasm was scanty and poorly stained. The cellular pattern was usually perivascular with varying degrees of intervascular necrosis, but in some areas there was an alveolar cellular arrangement.

8. Increased numbers of reticulin fibrils were present in all cases, usually in relation to vessels, in areas of leptomeningeal invasion, or in regions containing collagenous connective tissue stroma. It appeared doubtful that a significant portion of the reticulin was produced by the neoplastic cells.

9. Reactive and degenerating astrocytes were frequently present in and surrounding the neoplasms.

10. Numerous microglial cells in all stages of activity were scattered throughout the tumor and did not appear to be an integral part of the neoplasm.

11. It is suggested that this neoplasm arises from an undifferentiated mesenchymal perivascular cell which is normally present among the connective tissue elements surrounding blood vessels and capillaries and that the term perithelial sarcoma be retained, the group so designated to include those similar neoplasms which have been classified variously as alveolar sarcoma, perivascular sarcoma, reticulum cell sarcoma, microglioblastoma, and primary reticuloendothelioma.

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LACK OF BEHAVIORAL EFFECTS FOLLOWING DESTRUCTION OF SOME THALAMIC ASSOCIATION NUCLEI IN MONKEY

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NEUROPSYCHOLOGICAL studies on the monkey's association cortex have demonstrated that various behavioral effects may be produced by ablating different cortical regions. These behavioral changes are not strictly localized in discrete areas; instead, certain behavioral disturbances tend to follow the damage of one particular region more consistently than damage to other regions. Thus, visual discrimination learning is disturbed by temporal neocortical ablation, although occasionally also by prefrontal lesions. The efficiency of performing somesthetic discriminations and the conditional reaction problem is impaired by lesions in either the parietotemporal or the prefrontal area. The ability to do the delayed reaction problem is almost completely lost after prefrontal removal but is only infrequently and slightly retarded after preoccipital and temporal extirpations (for references to the literature on this subject, see the review by Chow and Hutt [1]). Furthermore, these behavioral changes seem to result from the cortical damage alone; they are not correlated with degrees of retrograde degeneration in either thalamic relay or thalamic "association" nuclei.* This last finding seems to be paradoxical. It is known that there is an orderly projection from different parts of the association nuclei to different areas of the cortex. If a certain behavioral disturbance always follows the damage to a cortical area, then such disturbance should also correlate with the retrograde thalamic degeneration resulting from lesions in that area. However, the cortical projection fibers of different parts of the association nuclei are not equal; i. e., a small nuclear mass may project to a large cortical field and vice versa. Thus, it is possible that the severity of symptoms following cortical lesions may not be correlated with the extent of thalamic degenerations. This lack of correlation implies some sort of independence of functions between thalamic nuclei and their cortical projection fields. A clear demonstration of such a dissociation may cast doubt, as far as its behavioral correlates are concerned, on the significance of the so-called thalamocortical reverberating circuits.

The present experiment is an attempt to examine the effects on behavior following lesions placed in the two principal thalamic "association nuclei" of monkeys, i. e., n. medialis dorsalis and n. pulvinaris. These two nuclei are studied for the following reasons: 1. They are the most prominent "association nuclei" projecting to large parts of the association areas. 2. Their cortical projection plans have been mapped out: N. medialis dorsalis projects to the prefrontal cortex [4] and n. pulvinaris to the parietotemporopreoccipital region.[5] 3. Corticofugal fibers of these

From the Yerkes Laboratories of Primate Biology, Inc.

* Footnotes *2* and *3*.

nuclei probably also exist, although their courses and terminations have yet to be definitely determined.[1] 4. Behavioral tests are available which are diagnostic for lesions within the various parts of the cortical fields of these two nuclei. By using these same tests, and by making lesions directly in the "association nuclei," it was hoped that behavioral changes equivalent to those resulting from the removal of different parts of the association areas might be obtained. Such data are pertinent in evaluating the importance of the thalamocortical circuits in behavior. If the integration of such circuits is essential for normal behavior, then similar disturbances should appear after destroying either end of the circuit; i. e., the integration would be disturbed equally by either the ablation of a certain part of the association area or by damage to the nuclear division projecting to this area.

METHODS

Seven immature monkeys (Macacus mulattus) were the subjects of this experiment. They were trained on a series of behavioral tests both before and after surgery. Five tests were used. There were two visual tests: a color discrimination, a red plaque (positive) *vs.* a green plaque, and a pattern discrimination, a black diamond on white background (positive) *vs.* black and white horizontal striations. One somesthetic test was given: roughness discrimination, Grade 3 sandpaper (positive) *vs.* Grade 0000 sandpaper. Spatial delayed response was the fourth problem; the subjects were required to choose that one of two identical cups under which a piece of food had been previously shown. The last test was an auditory-visual conditional reaction; the animals were trained to select one or the other of two visual stimuli (red or green), depending on whether or not a bell (or in some cases a 1,000 cps tone) was sounding. The general procedure, apparatus used, and specifications of the stimuli have been reported in earlier communications from Yerkes Laboratories; Chow described the methods of testing visual discriminations and the delayed-response problem[6]; Blum, the roughness discrimination,[7] and Evarts, the auditory-visual conditional reaction.[8]

All seven animals were trained on the color and pattern discriminations and the delayed-response problem. Six of the animals (excluding Monkey 7) were tested for the auditory-visual conditional reaction. Only three of the seven subjects were trained on the roughness discrimination test (Monkeys 1, 2, and 5). In addition, notes on the "personality" and general cage behavior of these animals were kept throughout the experimental period.

After completion of the training, a preoperative retention test on the auditory-visual conditional problem only was given after a period of two months. Retention scores for the other tests are available from previous studies. The animals were then subjected to surgery. All operations were performed under pentobarbital (Nembutal) anesthesia, with aseptic technique. Multiple electrolytic lesions were made in the thalamic nuclei with the Horsley-Clarke apparatus. A unipolar anode electrode with direct current of 3 ma. for a period of one minute was used. For Monkeys 1 to 4 the placements of the electrodes were primarily aimed at n. pulvinaris. For the other three animals (Monkeys 5 to 7) lesions were made in both n. pulvinaris and n. medialis dorsalis. The maps of stereotaxic coordinates used in making these lesions were those of Atlas and Ingram[9] (Monkeys 1 and 2) and of Olszewski[10] (Monkeys 3 to 7).†

Postoperative testing started 14 days after surgery. The animals were killed immediately after the retraining. Their body weights at the time of killing were as follows: Monkey 1 (male), 2.7 kg.; Monkey 2 (male), 3.2 kg.; Monkey 3 (male), 3.0 kg.; Monkey 4 (male), 3.8 kg.; Monkey 5 (female), 3.0 kg.; Monkey 6 (male), 3.6 kg., and Monkey 7 (female) 2.5 kg.

The brains of these animals were perfused and fixed in 10% formalin, dehydrated in alcohols, and embedded in nitrocellulose. Coronal sections of 25 μ thickness were cut through the hemi-

† Dr. H. W. Ades, chairman of the Department of Anatomy, Emory University, allowed me use of the facilities of his laboratory; Dr. W. A. Mickle, of the same department, aided in making the lesions in Monkeys 1 to 6; Drs. K. H. Pribram and M. Mishkin, of the Institute of Living, cooperated in the operation on Monkey 7.

spheres of Monkeys 1, 2, and 6, and of 50 μ thickness through the hemispheres of Monkeys 5 and 7. The brains of Monkeys 3 and 4 were sectioned horizontally at 50 μ thickness. Every 10th section was saved and stained with thionine in those brains cut at 50 μ thickness, and every 20th section was stained in the brains cut at 25 μ thickness. Outline drawings of the stained sections were made with a projector. The thalamic lesions were examined under the microscope and plotted on these drawings. The total areas of the thalamic nuclei and the lesion within it were estimated by using a cross-hatched eyepiece, checked with a stage micrometer. The proportions of damaged area of the two nuclei (n. pulvinaris and n. medialis dorsalis) were calculated for each of the stained sections. The mean of the proportions for all sections through a nucleus gives an estimate of the percentage of destruction of the nucleus.

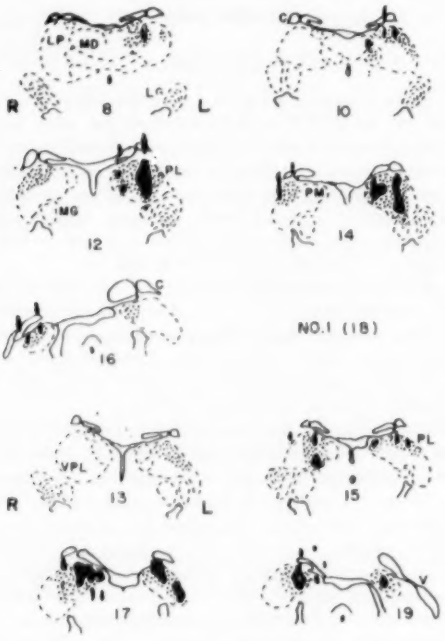

Fig. 1.—Drawings of the stained cross sections through the thalamic lesions of Monkeys 1 and 2. Thalamic lesions are indicated by solid black (central necrotic area) and stippling (surrounding area of gliosis). Index numbers under each section indicate the number of stained sections through the dorsal thalamus rostrocaudally. The number in parentheses gives the total number of stained sections through the thalamus. *AM*, n. anteromedialis; *LP*, n. lateralis posterior; *MD*, n. medialis dorsalis; *LG*, lateral geniculate body; *MG*, medial geniculate body; *PL*, n. pulvinaris lateralis; *PM*, n. pulvinaris medialis; *PI*, n. pulvinaris inferior; *VL*, n. ventralis lateralis; *VPL*, n. ventralis posterolateralis; *V*, ventricle; *R*, right; *L*, left.

RESULTS

Anatomical Data.—Figures 1, 2, and 3 show either the cross sections (Monkeys 1, 2, 5, 6, and 7) or the horizontal sections (Monkeys 3 and 4) through the thalamic nuclei of the subjects. Only the alternate stained section through the lesion is depicted here. Owing to the great individual variations in the dimensions of the skull and the difficulty inherent in using the Horsley-Clarke apparatus, in none of

the monkeys has a complete destruction of either n. medialis dorsalis or n. pulvinaris been achieved. There were unintentional damages of other thalamic nuclei, which were usually small and not relevant to the present study. Table 1 lists the estimated percentages of destruction of n. medialis dorsalis and n. pulvinaris, together with

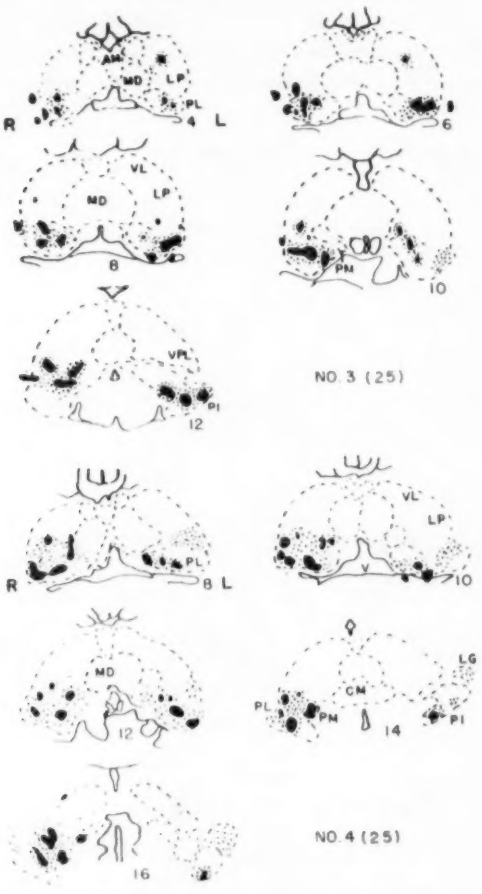

Fig. 2.—Drawings of the stained horizontal sections through the thalamic lesions of Monkeys 3 and 4. Index numbers indicate the number of stained sections through dorsal thalamus dorsoventrally. Other designations are similar to that of Figure 1.

those for any other thalamic nuclei that were involved, for each of the monkeys. It should be noted that about 20% of n. medialis dorsalis was destroyed bilaterally in Monkeys 5, 6, and 7. The largest lesions in n. pulvinaris are those of Monkeys 2 and 4, with about 50% bilateral destruction.

Both the strength and the duration of the direct current used in the present study (3 ma., 60 seconds) differ from those recommended by Carpenter and Whittier (5 ma. or less, 30 seconds).[11] Histologically, however, the resulting elec-

trolytic lesions are similar in character to those obtained by their method. The lesion consists of a central necrotic area surrounded by a band of glial and phagocytic cells. In the figures, the central areas are depicted in solid black and the surrounding regions in dots. The sizes and shapes of the lesions are varied and irregular, especially when several electrode placements are near each other and when there are possible vascular complications. In Monkey 7 there is a great enlargement of the inferior and posterior horns of the right ventricle and almost complete destruction of the posterior part of the right thalamus, including the entire n. pulvinaris.

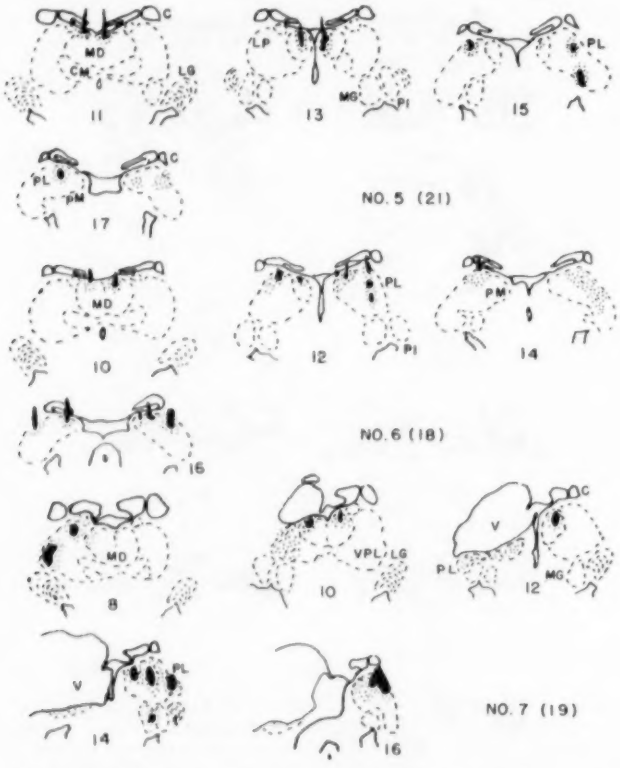

Fig. 3.—Drawings of the stained cross sections through the thalamic lesions of Monkeys 5, 6, and 7. Designations are similar to that of Figure 1.

Transient Effects and General Behavior Observations.—Immediately after operation five monkeys (1, 3, 4, 6, and 7) showed muscular weakness and awkward movements of their legs. Two animals (1 and 4) had additional partial paralysis of their left arms, and one (Monkey 4) had a left visual field defect. All these symptoms, with only one exception (Monkey 7), cleared up before the end of 14 days. The muscular weakness of the legs in Monkey 7 persisted throughout the testing period.

These transient effects were probably caused by the passing electrode tracts. All the electrode placements punctured both sides of the vertex of the central fissure in order to reach the thalamus.

TABLE 1.—*Percentages of Destruction of Nucleus Pulvinaris and Nucleus Medialis Dorsalis of All Animals, Together with Lesions to Other Dorsal Thalamic Nuclei* *

Monkey No.	Destruction of N. Pulvinaris, %		Destruction of N. Medialis Dorsalis, %		Lesions in Other Thalamic Nuclei	
	R	L	R	L	R	L
1	10	46	..	7	.....	CM, LD, LP, MG, VPL
2	52	47	..	..	LD, MG	LD
3	41	35	..	..	LP, MG, VL, VPL	LP, VL, VPL
4	63	42	8	..	CM, LP, MG, VL, VPL	LP, VPL
5	7	11	15	14	.....	.....
6	16	24	16	11	LP	.....
7	90	24	12	20	LD, LP, VPL, VPM	MG, VPL

* R indicates right thalamus; L, left thalamus; CM, centrum medianum; LD, n. lateralis dorsalis; LP, n. lateralis posterior; MG, medial geniculate body; VL, n. ventralis lateralis; VPM, n. ventralis posteromedialis; VPL, n. ventralis posterolateralis.

TABLE 2.—*Total Number of Trials and Errors Required by the Monkeys to Learn the Visual Discriminations, Roughness Discrimination, and Delayed-Response Problem* *

Monkey No.	Color		Pattern		Roughness		Delayed Response	
	T	E	T	E	T	E	T	E
1	130	48	150	49	190	97	660	227
	6	2	3	1	109	25	420	64
2	260	74	185	50	228	80	900	325
	60	15	60	13	94	30	510	111
3	120	39	187	57	...	..	570	190
	30	11	70	23	...	..	360	44
4	220	82	188	69	...	..	1,200	317
	60	17	68	22	...	..	420	59
5	213	79	94	34	211	83	450	98
	90	18	70	26	110	32	300	57
6	120	33	100	30	...	..	460	67
	30	5	70	21	...	..	300	32
7	200	88	187	57	...	..	...	...
	120	41	210	64	...	..	...	...

* The upper figure for each animal on each task is the preoperative score, and the lower one, the postoperative score. T indicates number of trials, and E number of errors.

There were no detectable changes in "personality" or general cage behavior in any of the animals after the operation.

Visual Discrimination.—Table 2 gives the preoperative and postoperative learning scores of all animals on visual discriminations, roughness discrimination, and the delayed-response problem. Preoperatively all monkeys learned the color dis-

crimination within the normal range.[12] The average number of trials required to reach a criterion of 20 successive errorless trials was 181, and the average number of errors, 63. After operation all subjects showed large amounts of saving in relearning. The amounts of saving in number of trials ranged from 40% to 95%, with a mean of 70%. The amounts of saving in errors ranged from 49% to 96%, with a mean of 76%.

Original learning scores of the pattern discrimination give a mean of 170 trials and 49 errors. Postoperatively, with the exception of Monkey 7, all the animals showed savings in relearning. The amounts of saving average 58% (range, 26% to 98%) in number of trials, and 61% (range, 25% to 98%) in errors. Monkey 7 took slightly more trials (112%) and errors (120%) than preoperatively to relearn this problem.

The degrees of postoperative saving in relearning the visual discriminations (except for Monkey 7 on pattern discrimination) are not different from retention scores of normal monkeys; these findings indicate a normal process of forgetting due to the lapse of time. The different amounts of saving by different animals are not correlated with the location and extent of the thalamic lesions. For example, the ability to perform these visual tasks is disturbed with temporal neocortical ablations; a cortical region receives projection fibers from the posterior part of the n. pulvinaris medialis.[5] This part of the pulvinar was almost completely destroyed in two monkeys of the present study (2 and 4), and yet both these animals gave about the same amount of retention as others, who had smaller lesions in this nuclei (Monkeys 3, 5, and 6).

Somesthetic Roughness Discrimination.—Only three monkeys (1, 2, and 5) were tested on this problem. Their learning scores are given in Table 2. All three animals showed saving in relearning this problem postoperatively. Again, the degree of saving is not correlated with the location and extent of lesions in the thalamic nuclei. Both Monkeys 2 and 5 showed a greater amount of saving than Monkey 1, although the latter had a smaller thalamic destruction.

Delayed-Response Problem.—Monkeys 1 to 6 were tested on 5, 10, and 15 seconds' delay, both without opaque screen and with an opaque screen covering the food cups during the delay intervals. The criterion used was 90% correct during a 30-trial session with each of the six delays. Preoperatively the mean total number of trials (including the criterion trials) of these six animals is 960, and of errors, 202. After thalamic operations all the animals had no difficulty in relearning this task; they showed saving in retesting scores. The amounts of saving in trials average 48% (range, 18% to 78%) and in errors average 56% (range, 26% to 82%). The degrees of postoperative saving on this problem are also not correlated with the extent of destruction in the n. medialis dorsalis. For Monkey 7 only 100 trials each were given on the 10- and 15-second delay intervals with the opaque screen. This animal's preoperative percentages correct were 83% for the 10-second delay and 71% for the 15-second delay. After the surgery, the scores were 91% and 67% correct, respectively.

Auditory-Visual Conditional Reaction.—Six monkeys were trained on this problem (excluding Monkey 7). The auditory cues used for Monkeys 1, 2, 5, and 6 were sounding a doorbell, and for Monkeys 3 and 4, a 1,000 cps tone with varied intensities generated from an audio-oscillator. The initial learning scores average

2,450 in total number of trials (range, 1,460 to 3,069); 426 in errors (range, 499 to 1,150); and 64, in reversals (range, 37 to 91). These scores are similar to those reported by Evarts for his normal monkeys. After the monkeys learned the problem, they were given 100 trials in which the two conditions were randomly mixed (i. e., a bell or a tone was sounded or not sounded, and the animals were required to choose green in the former condition and red in the latter). The percentages of correct responses made by the six monkeys (Monkeys 1 to 6) were 86, 80, 70, 80, 74, and 72, respectively. After approximately two months they were given another 100 mixed trials for the preoperative retention tests. The percentages correct for these retention scores were 76, 75, 74, 83, 78, and 70, respectively. Another 100 mixed trials were given after the surgery, and the percentages correct of the six animals' performances were 73, 71, 77, 84, 70, and 68, respectively. The slight differences between preoperative and postoperative percentages are not statistically significant.

COMMENT

The results of the present study indicate that bilateral destruction of portions of n. medialis dorsalis and n. pulvinaris does not appreciably affect either the monkey's general behavior or its ability to perform the specific problems tested. Good postoperative retention scores, similar to those of the normal monkey, were obtained in a total of 28 out of 29 formal training problems. The cause for the sole exceptional case, Monkey 7's failure to retain the pattern discrimination, is not clear. It is probably not due to the grossly enlarged ventricles of this animal, for she showed good retention at the same time on the other two problems (color discrimination and delayed response).

A full understanding of the significance of these negative findings must await further experimentation. The following points, however, merit brief discussions. It is conceivable that the lack of behavioral effects is because of the incompleteness of the lesions. With a total destruction of n. medialis dorsalis and n. pulvinaris, some behavioral symptoms might occur. Such an interpretation implies a high degree of equipotentiality of these nuclei and also a difference in functional organization between these nuclei and their cortical projection areas, for partial destruction of the latter is effective in producing behavioral disturbances. Although both the location and the extent of the thalamic injury vary from animal to animal, they are not correlated with the different amounts of postoperative retention. Whether there are critical minimal foci, together with their fringe zones, within the association nuclei responsible for different functions is not clear. The negative results obtained may be due to the fact that symptoms follow only the destruction of these foci, and damages to the fringe parts produce slight effects. However, almost the entire n. pulvinaris has been covered by lesions in one monkey or another in the present study. It is, therefore, questionable whether some critical foci may exist which were entirely missed by the surgery.

The possibility that the tests used are not sensitive enough to reveal behavioral changes cannot be definitely ruled out. These tests were chosen because of their value in differentiating variously localized lesions in the association areas. The retention of visual discriminations is disturbed by temporal neocortical ablation. The posterior n. pulvinaris medialis, which projects to this temporal cortex, was almost completely destroyed in Monkeys 2 and 4, who showed normal retention of

these tasks. Delayed-response performance is abolished after partial removal of the prefrontal area, which receives fibers from n. medialis dorsalis. This nucleus was partially damaged in Monkeys 5 and 6. Retardation in relearning roughness discrimination has been shown to follow both lesions of the parietotemporal region (to which the n. pulvinaris lateralis and n. pulvinaris inferior project) and extirpations of this region. The ability to perform an auditory-visual conditional reaction is impaired by surgery of the superior temporal gyri, especially the auditory areas. This task was included especially in the hope of examining the traditional view that the n. pulvinaris is one site for the formation of auditory-visual associations. Unless the behavioral effects following ablation of these two nuclei are entirely different from those after damage to their cortical fields, some disturbances in performing these tests were to be expected. The failure to demonstrate clear-cut behavioral changes in these animals, especially in Monkeys 2 and 4, probably cannot be explained by the inadequacy of the tests employed alone.

The results of the present study are in agreement with earlier reports,‡ which showed that the degree of retrograde degeneration of the thalamic nuclei is not correlated with behavioral symptoms following cortical ablations. Either the "association nuclei" do not participate in mediating behavior tested, or they alone, but not their projection fields, have a high degree of equipotentiality: Any remaining part may take over the function of the whole nucleus. These considerations point to a dissociation of functions between "association nuclei" and cortical association areas. They also raise the question of the functional validity of the so-called thalamocortical reverberating circuits. The integrity of such circuits may not be essential for mediating normal behavior.

SUMMARY

Seven immature monkeys (Macacus mulattus) were trained preoperatively on a series of learning problems. All animals learned two visual discriminations (color and pattern) and a delayed-response problem. Six of them (excluding Monkey 7) were trained on an auditory-visual conditional reaction, and three of these (Monkeys 1, 2, and 5) were trained also on roughness discrimination. Bilateral stereotaxic lesions were made mainly in n. pulvinaris on Monkeys 1 to 4, and in both n. medialis dorsalis and n. pulvinaris on Monkeys 5 to 7. Postoperatively, all animals (except Monkey 7 on pattern discrimination) showed normal retention in relearning these tasks. No permanent "personality" or general behavioral changes were observed. This lack of clear-cut behavioral effects following partial destruction of the "association nuclei" contrasts with symptoms obtained after partial ablation of the cortical association areas. The results are discussed in relation to the functional significance of the so-called thalamocortical reverberating circuits.

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Obituaries

MARGARET WILSON GERARD, M.D.
1894-1954

Dr. Margaret Wilson Gerard, 59, well-known child psychiatrist and psychoanalyst, died on Jan. 12, 1954, after a lengthy illness. She is survived by her husband, Dr. Ralph W. Gerard, and a son, James Gerard.

Dr. Gerard received her B.S. degree at Wellesley in 1920, her Ph.D. with Prof. Stephen Ranson in 1922 at Northwestern University Medical School, and her M.D. degree at Rush Medical College in 1924. Of most interest to neurologists are her original studies of the descending root of the fifth cranial nerve, the anatomy of which she worked out in great detail—and it is still valid. After an internship at the Children's Memorial Hospital, Chicago, she spent a year working with F. M. R. Walshe at the National Hospital for Paralyzed and Epileptics, Queen Square, London, and then started with Jung and Adler in Zurich and Vienna in 1927. Then there was a lengthy period of work with children at the Institute for Juvenile Research and the University of Chicago, culminating in special studies in 1935 with Anna Freud and Helene Deutsch in Vienna.

A pioneer in the field of child psychiatry, Dr. Gerard was well known in Europe and the United States as a teacher, practicing psychoanalyst, and author. In recent years her special interest was the study of the psychosomatic illnesses of children and treatment facilities for the emotionally disturbed child. At the University of Illinois College of Medicine she was active in the organization and operation of the Psychosomatic Ward of the Neuropsychiatric Institute.

Dr. Gerard was a past President of the Chicago Psychoanalytic Society, a consultant in child psychiatry to the World Health Organization, a member of committees of the Group for Advancement of Psychiatry, a member of the board of directors of the Jewish Children's Bureau in Chicago, a member of the council of the American Psychosomatic Society, and a member of the Chicago Child Care Committee.

Dr. Gerard will be remembered not only for her high professional attainments but also for her warm and sympathetic interest in her patients and many students. Her greatest joy apart from her work and human contacts was her beautiful home in Vermont, where she spent each summer for many years. Here she was able to relax and live for herself and her closest friends, all of whom will miss her greatly.

ROY R. GRINKER, M.D.

Special Article

AUTONOMIC FUNCTIONS OF THE DIENCEPHALON

A Summary of the Experimental Work of Prof. W. R. Hess

P. GLOOR, M.D.
MONTREAL, CANADA

RECENT years have brought forth an impressive wealth of new knowledge of the physiology of the subcortical structures of the brain. One of the most coherent and outstanding studies in this field is the experimental work of Prof. W. R. Hess, of Zurich. Unfortunately, none of Hess's publications have been translated, and it was felt, therefore, than an English summary of his studies on the autonomic function of the diencephalon deserved publication. The following summary was undertaken on the advice of many English-speaking neurologists and neurophysiologists who emphasized this need.

The central problem of Professor Hess's work was that of the functional organization of the diencephalon, which was investigated mainly by electrical stimulation in the unanesthetized animal. This method shows the positive aspect of the function of this structure. The lesion method, very commonly used elsewhere, has some shortcomings, due in part to the fact that after a lesion not only is there a negative effect, in other words, absence of a specific function, but there are more active changes, due to a compensatory rebalancing of the injured system, which makes a clear interpretation of the results very difficult. Therefore, the study of the effects of lesions, although not completely omitted, plays a minor role in Hess's work.

Much attention was paid to the possible understanding of the dynamic processes in the subcortex. There is always what Hess calls *ein Kräftespiel*, an interplay of forces, which, when in the state of balance, may simulate quietness or absence of activity. A shift in these forces and a change in the balancing mechanism give rise to externally apparent function. The more profound dissolution of these functions produced by lesions results in pathological syndromes.

METHOD

According to Hess's guiding principle of studying the function of the diencephalon in conditions as physiological as possible, most of the experiments were done on unanesthetized, freely moving animals with implanted electrodes. The only experiments performed with the animal under general anesthesia were those in which the function under study required techniques incompatible with free movements of the animal. This was the case, for instance, in all experiments in which blood pressure measurements were necessary.

All experiments were performed on the cat because of the relatively uniform size and shape of its brain and because its very expressive behavior is well known and easily studied. The electrodes used were thin, insulated, perfectly straight steel wires of a diameter of 0.25 mm. and with a bare tip 1 mm. in length. Two of these electrodes with tips 0.5 mm. apart were connected to one pole of the stimulator output and thus acted as a single electrode. Three of such twin electrodes were mounted 1.5 mm. from each other. We cannot go into

Based on a lecture given at the Montreal Neurological Institute.

From the Department of Neurology and Neurosurgery, McGill University Faculty of Medicine, and the Montreal Neurological Institute.

the details of the technique used to insert the electrodes. Hess has worked out his own method of electrode placement without using a stereotactic instrument and is able to locate them at the desired point with a high degree of accuracy.

We shall be somewhat more explicit about the parameters of stimulations used. This was a difficult problem to solve, to which Hess paid much attention. The diencephalon is a brain structure where, in a relatively small area, are closely interlaced nerve fibers of different anatomical and functional properties. Some react predominantly to stimuli with a sharply rising phase; others do not show this pronounced difference in reaction to sharply and slowly rising pulses. These latter are mainly the autonomic elements. This means that some fiber types accommodate easily, and some do not. This situation makes it important to determine for which stimulus these differences are minimal. This statement may sound academic; however, let us assume that one electrode is placed in a region where there are small, slowly reacting, autonomic fibers, but a short distance apart from it lies a fiber tract with larger, quickly reacting fibers of the somatic system. If we now use a stimulus with parameters for which the threshold of the autonomic fibers will be high and for which the threshold of the somatic fibers will be low, then the first, and probably the only, sign to appear will be that produced by the excitation of the larger somatic fibers. The threshold for the somatic fibers lying at a greater distance is already reached before the autonomic fibers, which lie in the very region where the electrode tips are located, can react. Use of stimuli with a sharply rising phase will give such preponderance to the sensorimotor somatic effect that stimulation has to be discontinued before the necessary time limit can be reached, when the slowly appearing autonomic effects become manifest. The observer, relating the effect to the site of the electrode tip, will, therefore, erroneously ascribe the effect to the region in which the electrode tips were located and which actually is not responsible for the observed effect.

That this difference of threshold is a real problem for certain wave forms is demonstrated by the fact that the ratios of average threshold, as worked out by Hess for the different fiber types, are very different when tested with faradic current, with square-wave pulses, or with pulses in which the rising and the falling phases are damped. The differences in threshold of the different fiber types are very high for the faradic current, less high for square-wave pulses, and considerably lower for damped direct-current pulses.

If the threshold for the ulnar nerve is designated as 1, the threshold for the cardiac branches of the vagus, when tested with faradic current, will be 22. It will be only 5 when tested with damped pulses. For the cervical sympathetic fibers, when faradic current is used, the threshold is 13 times as high as that of the ulnar nerve. It is 8 times as high when tested with square-wave pulses, whereas with damped direct-current pulses the threshold will be only 1.4 to 1.5 times that of the ulnar nerve. Faradic current is, therefore, the least adequate stimulus for subcortical stimulation. It should be noted, and Hess himself stresses this point, that the use of the damped pulse form does not mean that the autonomic system is stimulated in a selective way. It means only that the thresholds of the different systems are brought together as closely as possible.

The damped pulses used by Hess were direct-current pulses of a duration of about 12 msec., and in the intervals between them a low voltage current of opposite polarity was delivered through the electrodes in order to prevent polarization of the electrode tips. This small counteracting current does not produce excitation because the voltage is subliminal. The long duration of the pulses was criticized by Ranson and Magoun [1] and by Harrison,[2] who claimed that some of Hess's results might be due to electrolytic lesions. Hess himself has given much thought to this possibility and did experimental controls of this point. The complete recovery of the animals after stimulation and the histological controls exclude the possibility of electrolytic lesions. This, of course, holds true only as long as one follows certain precautions which have been outlined by Hess.

Especially high voltage stimulation has to be avoided. Hess used voltages as low as possible, beginning with intensities as low as 0.5 volts and progressing slowly to 1.0, 1.5, and 2.0 volts. Sometimes stimulation of 3.0 to 4.0 volts was used, but almost never more. These low voltages prevent the occurrence of electrolysis and of irradiation of stimulation to neighboring structures. The frequency of stimulation also was always low, ranging between 4 to 10 cps. Higher frequencies were avoided in order to distinguish between true tonic effects, which appear with low

frequency stimulation, and the effects of the tetanization of the effector muscles by high frequency stimulation. Lesions, when desired, were produced by an accurately controlled diathermy current.

Every experiment was filmed to allow reexamination of all interesting reactions once the histological controls were available. Anatomical studies were done on the brains of all the experimental animals, and the stimulated points were plotted in an atlas.

By this method the whole diencephalon was mapped in a series of about 380 cats and over a period of nearly 30 years. The effects of more than 3,500 stimulation points were studied.

STIMULATION EXPERIMENTS

1. *Concept of Ergotrope and Trophotrope Activities.*—This paper will not deal with the motor effects, which were mainly thalamic in origin.* We shall limit our discussion to the autonomic effects and those motor effects subserving vegetative functions. These effects were produced mainly from the hypothalamus, some adjacent parts of the thalamus, and the septal region.

Each functionally defined structure within the nervous system is considered to be an integrating mechanism, which when acting will produce neither a mere single effect nor a more or less random association of effects, but will display very well-organized patterns of action, all directed toward the aim for which the functions are devised. Every excitation will induce within the nervous system a certain pattern of activity involving a variety of mechanisms, all of which are related to the performance of a certain definite act. An effect produced by localized stimulation might be more prominent than others, but it will not be isolated; it will be associated with other responses of an organized, purposeful functional pattern. The central nervous system has very complex patterns of organization, but this whole integrated complexity can be seen only when we study the freely moving, unrestrained, and unanesthetized animal. Anesthesia always dissolves to some extent the highly organized integration.

On the autonomic level the organism has to face two main tasks. The first one consists in providing the organization of all mechanisms giving the animal the necessary background enabling it to display an externally directed behavior, e. g., in fight or flight. This first type of function subserves the purpose of action; it is what Hess calls "ergotrope," and its autonomic effects are mainly mediated in the periphery by the sympathetic nervous system. An ergotrope type of activity is, for instance, that of physical effort, with all its somatic and autonomic components.

The second type of function subserves the purpose of restitution and economy of energies. It acts mainly through protective mechanisms providing the necessary rest, thus avoiding overstrain and exhaustion. It also activates all mechanisms concerned with the ingestion and assimilation of food. This second mechanism is a necessary counterpart of the first and is called the "trophotrope-endophylactic" system, and its peripheral mediator is mainly the parasympathetic nervous system.

Both functional systems are not purely autonomic in the strict sense, for they are not mediated in the periphery only by either the sympathetic or the parasympathetic nervous system. They always involve more or less somatic effectors also, the best example for this being respiration, which in its functional character is truly vegetative and yet is mainly mediated by somatic effectors.

* A detailed monograph, "Autonomic Function and Extrapyramidal Function," by Dr. W. R. Hess himself, including these motor effects, will soon be published by Grune and Stratton, Inc., New York.

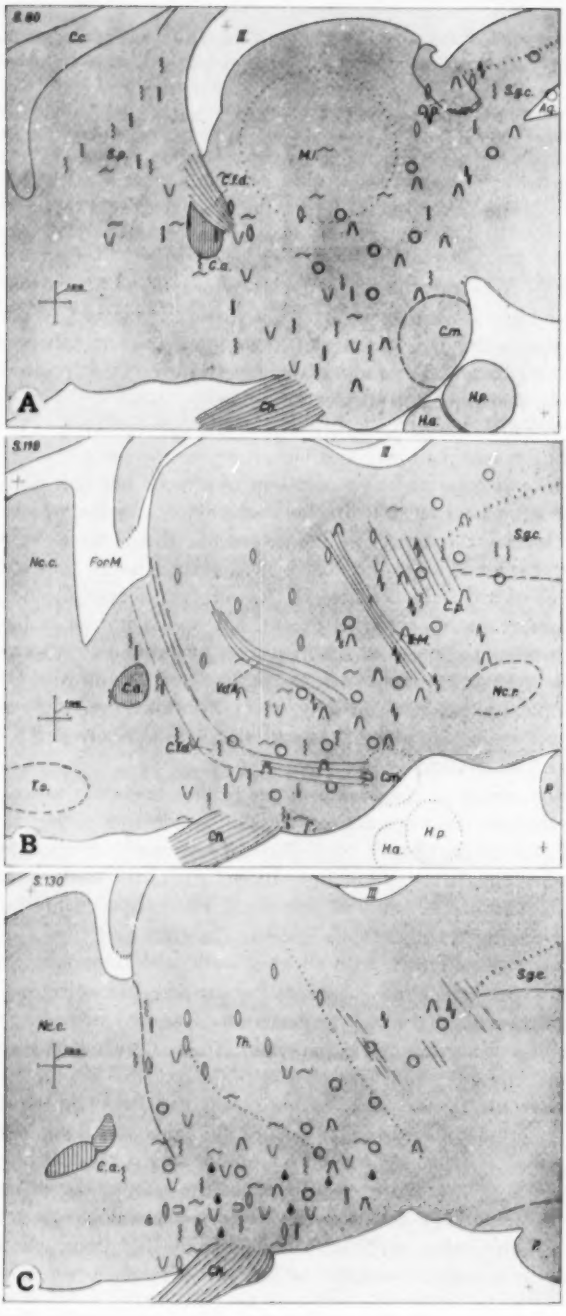

Figure 1

(See legends on opposite page)

To these two types of autonomic functions correspond two rather distinct areas of the diencephalon, each of them organizing either ergotrope or trophotrope activities. To illustrate this, let us start with a very simple example. The size of the pupil indicates in a simple and obvious way the state of balance between the ergotrope and the trophotrope system. A wide pupil will indicate an ergotropically oriented activity, a narrow pupil a trophotropically oriented one. This is an oversimplification, but under otherwise constant conditions, as far as the intensity of light reaching the retina is concerned, this statement is true. A shift from an ergotrope to a trophotrope activity will manifest itself in a variation in the size of the pupil. Stimulation of the diencephalon will produce either effect, pupillary dilatation or pupillary contraction, but these two effects are produced from two distinctly different zones. The one yielding dilatation extends from the midbrain-diencephalic transition zone forward into the hypothalamus in a parasagittal plane about 2 mm. from the midline. More medially and more laterally, the points producing pupillary dilatation are scarcer. The zone is rather sharply demarcated behind the preoptic region. It lies on the base and does not merge into the thalamus. The opposite effect, pupillary contraction, will be produced by stimulating a zone which lies more dorsally in the basal thalamic region, and also anteriorly and more laterally in the lateral supraoptic and preoptic region.

This arrangement in itself is not very surprising, but the problem becomes more interesting when we consider not only the pupillary effects but also the responses which might be associated with them. When a pupillary active stimulus happens to stimulate a subcortical motor fiber tract, there will be muscular twitches synchronous with the stimulating pulses. These twitches will increase in amplitude when the pupil dilates and will decrease in amplitude when the pupil becomes narrow. This means that pupillary dilatation is associated with facilitation of muscular activity and pupillary constriction is associated with motor inhibition. Moreover, the pupillary dilatation may be accompanied by a state of general excitement of the animal, and the pupillary constriction, by a quieting down of the animal, which eventually goes to sleep. When the stimulation is carried out in the lateral supraoptic and preoptic region, the pupillary constriction will be accompanied by a state of generalized loss of muscular tone. This state, called adynamia by Hess, is characterized by the fact that the animal sinks down like an inert mass and no readjusting movements are seen, so that it finally takes a random and quite unnatural position (Fig. 2).

EXPLANATION OF FIGURE 1

Fig. 1.—Parasagittal section through the diencephalon. *A*, 0.8 mm. from the midline; *B*, 2 mm. from the midline; *C*, 2.8 mm. from the midline. Ergotrope responses: ∩ indicates increase in blood pressure; ∿, activation of respiration; O, pupillary dilatation. Trophotrope responses: ∪ indicates fall in blood pressure; ∼, inhibition of respiration; 0, pupillary constriction; ≀, micturition; ⋮, defecation; ●, salivation; ↄ, vomiting.

Note that ergotrope effects tend to be grouped in the posterior hypothalamus and are densest in a plane about 2 mm. from the midline. The trophotrope effects tend to be grouped in the more anteriorly and laterally placed areas.

From Hess, W. R.: Das Zwischenhirn, Basel, Benno Schwabe & Co., 1949.

These facts already show that we are dealing not with isolated effects but with associated functions which from one single point of stimulation are elicited together, even when every care is taken to avoid spread of current.

Within the area producing pupillary dilatation other signs of ergotrope character are elicited, e. g., a rise in blood pressure. This has about the same topographical distribution as the pupillary dilatation, perhaps not reaching so far forward in the hypothalamus. Many of the points from which the arterial blood pressure may be raised will on stimulation also produce an increase in pulse rate.

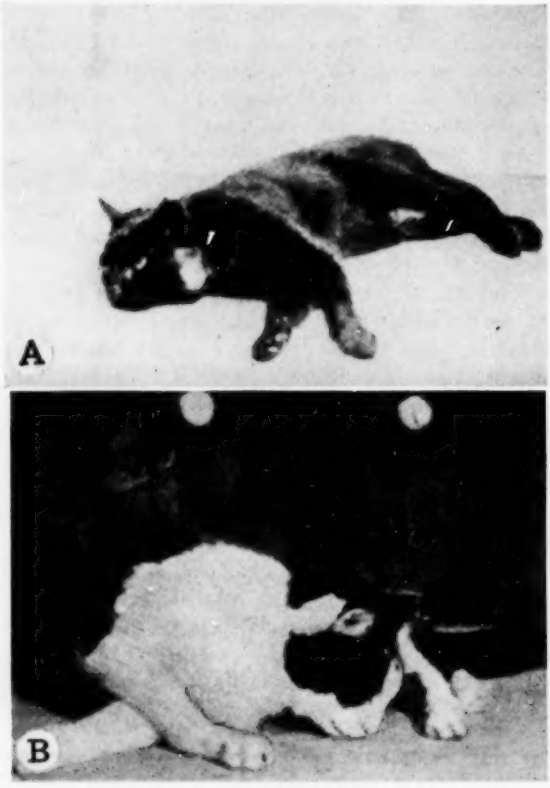

Fig. 2.—Adynamia as produced by stimulation in lateral preoptic and lateral hypothalamic areas. *A*, complete atonia; eyes are kept open. *B*, the animal is sunken down in an unnatural posture. No attempt is made to place the extremities in a normal position.

From Hess, W. R.: Das Zwischenhirn, Basel, Benno Schwabe & Co., 1949.

On the contrary, a fall in blood pressure is obtained from the anterior lateral hypothalamus, where points for pupillary constriction and adynamia are found. A drop in blood pressure is also produced from the basal thalamus, where pupillary constriction is obtained, and, in addition, medially in front of the chiasm in the preoptic region, and from there upward into the posterior part of the septum. In many of these points, especially in the septal region, the drop in blood pressure is associated with a decrease in pulse rate.

These effects upon the circulatory system fit very well with those observed on respiration. Here, again, we find activation subserving the ergotrope needs in those zones which display ergotrope effects. Activation of respiration, consisting of progressive increase of frequency and depth of respiration, as normally observed, for instance, in muscular effort, is seen when a zone extending from the midbrain-diencephalic transition zone into the posterior hypothalamus is stimulated. The most active points lie lateral to the entrance of the Sylvian aqueduct, in the region of the nucleus of the posterior commissure. It is to be noted that despite the constancy of the stimulation parameters this response always increases in intensity during stimulation, as physiologically the respiration does during a muscular effort. This type of respiratory response is not found as far rostrally as the other ergotrope responses we have considered; it occurs only in the posterior part of this zone.

In the anterior part of the region producing ergotrope responses is found another type of respiratory effect, which in the anesthetized animal is characterized by a sudden increase of the rate and which was called paroxysmal tachypnea. In the unrestrained and unanesthetized animal this type of respiration is not clearly seen, but from the same region are obtained similar responses which are associated either with a rage reaction of the animal or, in more laterally and anteriorly placed spots, with panting. Both types of activity will be considered later.

In the region giving trophotrope responses, i. e., the basal thalamus, the lateral subthalamic region, and the lateral and medial anterior preoptic region, there is obtained an inhibition of respiration, sometimes with respiratory arrest. In the most medial parts of this inhibitory field the effect very often is arrest of respiration. A peculiar type of respiratory inhibition is sometimes seen in the adynamia zone, as well as in the lower medial part of the massa intermedia, and this inhibition looks like real dyspnea. The respiration slows down, the inspiratory phase is prolonged, and the auxiliary respiratory muscles are brought into action. It is quite possible that this type of respiration is not an immediate effect of stimulation but a mediate one, being itself a consequence of a bronchospasm, which might represent the true immediate effect of stimulation. This reaction might, therefore, be considered as a centrally induced bronchial asthma.

2. *Organization of the Ergotrope Zone* (Fig. 1).—When we summarize this first series of results, certain definite statements about the localization of the ergotrope active points can be made. They lie in a zone extending from the transition zone between midbrain and diencephalon rostralward into the hypothalamus, occupying a rather narrow U-shaped zone around the lateral walls and the floor of the third ventricle. The most active part of this zone comprises the posterior hypothalamus. This zone produces such responses as pupillary dilatation, a rise in blood pressure, increase in pulse rate, activation of respiration, increase in motor excitability, and general excitement of the animal. Within this region there are no foci where specifically one of these effects may be produced with the exclusion of the others. This means that there is a collective representation of a group of functions acting as a purposeful synergic functional unit to bring together different effectors. All single effects are part of a global activation enabling the free display of an externally directed behavior; they all subserve well-defined autonomic needs of the organism, such as are required, for instance, during a muscular effort in defense, attack, or flight. This has led Hess to call it the "dynamogenous" zone of the hypo-

thalamus. The demarcation of this zone is not very sharp. There is at the boundaries some overlapping with points active in the opposite way, which accounts for some intermingling in these regions of trophotrope and ergotrope elements.

3. *Trophotrope Activities Related to Protective Mechanisms and to Digestive and Excretory Functions.*—The topographical distribution and organization of the points which on stimulation give trophotrope responses are a little more complicated, and before discussing them we have to add some other effects belonging to this group.

There is, first, salivation, which is very often produced, but which is not very easy to evaluate in its true significance. Salivation responses are obtained from a rather widespread zone, reaching from the septum and the preoptic area through the lateral and dorsal hypothalamus as far back as the central gray matter in the rostral midbrain. This same region also produces panting. This is a very interesting fact, for it shows again how a certain part of the diencephalon coordinates various effectors in order to carry out a definite performance. It is well known that panting in dogs is a very important thermoregulatory mechanism, which accomplishes what sweating does in other animals. It is less well known that the cat uses the same physiological mechanism as the dog. Panting is a rapid breathing with open mouth accompanied by salivation. The saliva evaporates and produces the loss of heat necessary to keep the body temperature stable. This effect, and even the usual sitting posture of the panting animal, is exactly reproduced by the electrical stimulus. The fact that Magoun and his collaborators [3] obtained the same effect by local heating of the responsive zone, using a noninjuring diathermy current, may suggest that this zone is normally activated by a rise in blood temperature and would, therefore, represent an intracerebral reflexogenic zone, comparable in some way to the bulbar respiratory center.

In another zone salivation has quite a different meaning. It is associated there with licking and chewing movements. However, two types of licking and chewing mechanisms must be distinguished, one being really related to the ingestion of liquid or solid food and the other looking rather like a protective mechanism, as though the animal were trying to get rid of a foreign body in its mouth. To these two different types of reaction correspond two different regions of localization. The first type, subserving the ingestion of food, is elicited from the ventromedial thalamus, the internal capsule, and the bed of the stria terminalis; the second type, subserving probably the removal of a foreign body from the mouth, is represented in more anterior parts of the licking zone in the septal area. Both of these reactions are also physiologically associated with salivation, and here again we have a good example of true coordination as a characteristic function of the diencephalon. The septal points seem to produce protective reactions or reactions subserving the function of getting rid of something uncomfortable. The same general principle holds true for sneezing, which is sometimes produced from this region. Furthermore, profuse salivation may be produced from the lateral hypothalamus, which does not seem to be associated with more complex activities and the true significance of which is not clearly understood. A viscous saliva, not secreted on stimulation of the points mentioned so far, is produced during a rage reaction, which occurs when the perifornical area of the hypothalamus is stimulated.

Vomiting, which is another parasympathetic and protective mechanism, is seen when the lateral supraoptic region and the hypothalamus lateral to the mammillary bodies are stimulated. This is true vomiting, with emptying of the stomach. A response which is more like retching than true vomiting is produced from the basal part of the ventral thalamus. It is probable that this latter effect depends upon excitation of sensory fibers coming from the mouth and from the throat.

Also trophotrope in character are those functions of emptying the bladder and the rectum which can be elicited from the diencephalon. Here, again, is a good example of true integration of somatomotor and autonomic activities into a purposeful act. Stimulation very often produces a well-organized pattern of behavior, such as is seen in the normal cat. The animal begins to move around, then takes the adequate position for micturition or defecation; finally the abdominal muscles go into action, the sphincters are released, and the content of bladder or rectum is expelled. It is an interesting fact that a circumscribed electrical stimulus can produce the whole complex pattern of behavior. The points which when stimulated lead to defecation or micturition lie in the septum or the bed of the stria terminalis. From these points the act is practically always carried out in the well-integrated manner described. More posteriorly in the lateral hypothalamus, and even in the lateral part of the central gray matter surrounding the Sylvian aqueduct, these responses are still obtained. From these latter areas, however, the animal oftener just expels the content of its bladder or rectum without taking the adequate posture. But even when stimulated here, the whole organized sequence of events as it occurs spontaneously in the normal animal is sometimes seen.

In the hypothalamic zone everything seems to happen more quickly. It is as though the hypothalamus acts more directly on the autonomic part of the mechanism and as though the cat is often surprised by the suddenness of its urge and has no time to get into the adequate posture. It sometimes happens that the animal takes the adequate posture only after it has voided or defecated, again suggesting that the hypothalamus acts more directly upon the autonomic effectors. On the other hand, the septum seems to activate first the motor components of the whole pattern; here the first reaction to the stimulus is, indeed, that the animal takes the adequate posture, and only after a fairly long delay does micturition or defecation actually occur. The micturition and defecation responses give other clues to the understanding of the action of the diencephalic integrating mechanisms. Micturition and defecation never occur together on stimulation of a point in the septum which can produce either micturition or defecation. Which of the two organs responds will depend on the state of filling of each; it will depend upon what Hess calls the vegetative proprioceptivity. The latency of the responses will be shorter if the hollow organ involved is filled. The filling of the organ makes it ready to react, and the central stimulation activates a latent urge. This illustrates very clearly how centrally induced nervous excitation is conditioned, directed, and modified by the activity of peripheral receptors, and how centers and periphery act as an integrated unit. Hess thinks that these peripheral mechanisms are very important for the correct timing of all the different single components of the whole integrated act.

4. *Sleep.*—Before summarizing the responses of trophotrope-endophylactic character, we shall include here another stimulation effect, which by its very nature is perhaps the purest trophotrope activity—that is, sleep. This effect will be dis-

cussed in a little more detail, not only because it has given origin to some controversy, but also because Hess's experiments and their interpretation are certainly one of the most valuable contributions to the complex and still poorly understood problem of sleep.

Sleep is a difficult thing to deal with experimentally. Many experimentally produced states look like sleep, although they may have actually nothing to do with true sleep. The difficulty arises from the fact that, looked upon from outside, sleep seems to be mainly inhibition, the absence of certain functions, which is the case also for the sleep-like states. It must be remembered, first, that inhibition is as truly a function of the nervous system as excitation, and, secondly, that no normally occurring nervous mechanism is only excitatory or only inhibitory; there is always some combination of the two. Inhibition in sleep is not the whole story. When we awake from a good sleep, we feel refreshed and our nervous strength is restored. This subjective feeling is without any doubt the expression of important processes of

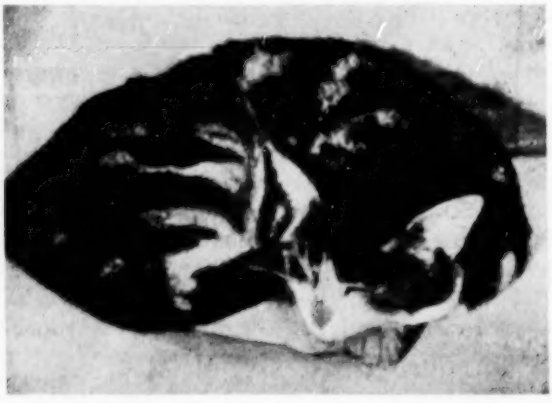

Fig. 3.—Sleep produced by stimulation in the hypnogenous zone of the thalamus. The animal shows the characteristic posture of a sleeping cat. Note the active contraction of m. orbicularis oculi.

From Hess, W. R.: Das Zwischenhirn, Basel, Benno Schwabe & Co., 1949.

restitution which have gone on in the central nervous system, the exact nature of which is not yet understood. But this restitution at least proves that sleep is not mere inhibition; sleep-like states, such as general anesthesia, do not show evidence of such restitutive processes. Sleep is a well-organized pattern of nervous activity where inhibitory and excitatory phenomena are integrated in such a way as to assure the optimal conditions for all processes of restitution in the body. It is in this sense the most truly trophotrope activity.

To make sure that an experimentally produced state is true sleep and not mere coma, stupor, anesthesia, etc., one must know that this state meets the criteria of true sleep. Such criteria have to prove more than the absence of some obvious function; they have to prove the existence of the positive forces present in natural sleep. Fortunately, nature has provided us with signs which are expressive of these positive processes. The closure of the eye, for example, in true sleep is not a mere relaxation of the levator palpebrae, as in a third nerve paralysis; it is a true tonic

contraction of the orbicularis oculi (Fig. 3). Such a tonic phenomenon expresses the existence of excitatory processes during sleep, and they have to be present if the condition is true sleep. Another sign of the same significance is the miosis, which is more pronounced than what might be observed after section of the cervical sympathetic fibers. There is true contraction of the sphincter of the iris, not mere paralysis of the dilator. This becomes even more evident when one considers that, according to the laws governing the simple pupillary reflex, closure of the eye should have the opposite effect, i. e., a dilatation of the pupil due to decreased illumination of the retina. The sleep mechanism thus acts in opposition to the pupillary reflex. This strongly indicates the existence of a positive central steering mechanism in sleep, leading to a progressive closing off of the organism from external sources of excitation. The functional readiness of the eye to react to external stimuli is lessened; hence there is active closure of the lids, active narrowing of the pupil, and active protrusion of the nictitating membrane.

Important criteria of true sleep are also the postural phenomena involved in it. A normal cat when going to sleep will take a certain posture. It will sit or lie in the beginning, with the head still raised. It will begin to close its eyes, to purr, and finally will settle down in a comfortable position. If the surrounding temperature is not high, it will curl up in order to protect itself against heat loss during sleep (Fig. 3). This curled posture requires active tonus of certain muscular groups. These active tonic phenomena are even clearer in the horse, which sleeps in a standing position, or in birds, which sleep standing on one leg. This well-organized distribution of muscle tone is also illustrated by the fact that the sphincters of bladder and rectum never relax during natural sleep.

Another criterion of true sleep is its reversibility. Strong enough sensory stimuli will arouse a sleeping subject; without this reversibility there is no true sleep. Of course, the obvious fact of loss of conscious contact with the surroundings should be included among the sleep criteria. There are also autonomic characteristics, such as, for example, the general decrease of the cardiorespiratory output. Finally, true sleep should produce a typical sleep pattern in the electroencephalogram.

Only if a state produced by stimulation is able to meet all these criteria of true sleep is one entitled to claim that stimulation has produced sleep, and not some kind of stuporous state. Most of the sleep responses obtained by Hess fulfill these requirements. Some others do not, and, when checked anatomically, the points stimulated then usually lie outside the zone where true sleep is induced. This is the case, for example, for the adynamia already mentioned, which obviously is not sleep (Figs. 2 and 3).

The region where true sleep may be produced, the so-called "hypnogenous zone," according to Hess, lies in the thalamus, beginning about 2 mm. lateral to the midline and extending somewhat laterally. It is located at the level of the massa intermedia in the horizontal plane, and in the anteroposterior direction between the mammillothalamic fascicle and the habenulointerpeduncular tract. It corresponds approximately to the region of the intralaminar nuclei.

To produce sleep only low voltage, low frequency stimulation is adequate. Drowsiness may already result from the mere mechanical stimulation of implanting the electrodes. Low voltage stimulation, of 0.5 to 1 or 2 volts, at a low frequency of 4 to 8 per second and for a duration of about 30 seconds, will induce drowsiness

or deepen it when already present. When such stimulations are repeated at intervals of about one minute for two to three times, the animal will finally settle down and go to sleep, displaying all the true sleep characteristics. In doing so, the animal will observe, as in natural sleep, the normal time course of events. There is much reason to believe that this slowness of onset of sleep is due to the antagonistic activity of peripheral receptors, producing a constant inflow of sensory impulses, and perhaps also to the activity of higher associative centers. This allows only a gradual decrease in activity and responsiveness, and step by step the sensory and motor contact of the organism with its surroundings is dissolved. This is not astonishing, for, as we all know, this is how we also go to sleep. Such an animal put to sleep artificially will sleep for hours when left undisturbed, and this maintenance of sleep does not require further stimulations. It will awaken spontaneously after this period, or it may be aroused by sensory stimuli of sufficient intensity. The most effective stimulus seems to be the smell of meat. The animal aroused in such a way will, after the sensory stimulation is removed, usually resume its sleeping position and go on sleeping. After having awakened spontaneously, the animal behaves normally and does not show any evidence of deficit. Sleep may also be interrupted by a stimulation carried out in the dynamogenous zone in the posterior portion of the hypothalamus, which is the rostral part of the brain-stem-activating system.

These experiments prove that true sleep can be produced by stimulation within the nervous system provided one observes certain precautions. The total reversibility of the response, the low voltage used throughout all experiments, and the absence of lesions in the histological sections refute the criticisms, brought forward by Ranson and Magoun [1] and Harrison,[2] that these effects were actually not due to stimulation but were the result of electrolytic lesions.

5. *Organization of the Trophotrope Zone* (Fig. 1).—When we try to summarize the effects of trophotrope-endophylactic character, we cannot give as clear-cut a picture of their topographical organization as was possible for the ergotrope system. There is no homogeneous zone which might be called the "antidynamogenous" zone, in analogy to the dynamogenous region. In opposition to the effects produced by stimulation of the ergotrope system, there is here some topical organization. There is, for instance, a clearly regional organization responsible for defecation and micturition, extending from the septum into the lateral hypothalamus. The lateral basal thalamus produces mainly miosis. There is only one zone which might be considered as being the region antagonistic to the dynamogenous zone, and in which is found the same type of collective representation of responses. This is the lateral anterior hypothalamus and the neighboring part of the preoptic area. Here we find a collective representation of such functions as pupillary contraction, slowing of respiration, drop in blood pressure, vomiting, salivation, micturition and defecation, and muscular adynamia. This region induces reactions which release tension by diminishing the capacity of the organism to produce physical effort. This seems to be the meaning of the linkage of the true autonomic parasympathetic effects with the inhibition of muscle tone, as seen in adynamia.

Other trophotrope mechanisms have more specific functions. They act as protective mechanisms of organotropic character and are physiologically activated from receptors usually located in the walls of hollow organs, like the bladder and the rectum.

6. *Behavioral Effects* (Fig. 4).—In addition to these autonomic functions of the hypothalamus, some highly integrated behavioral patterns are produced from this region which are expressive of an instinctively guided behavior or of emotional drives.

The sniffing response, which subserves the search for food, is obtained on stimulation of the medial forebrain bundle from the tuberculum olfactorium backward into the anterior portion of the hypothalamus lateralis. The cat goes around sniffing the floor. Other sniffing responses of a different character are obtained from the stria medullaris, the rostromedial thalamus, the bed of the stria terminalis, the dorsal septum, and the gyrus genualis. Here the cat sniffs around in the air and does not hold its head down on the floor. It is as though it were aware of a smell.

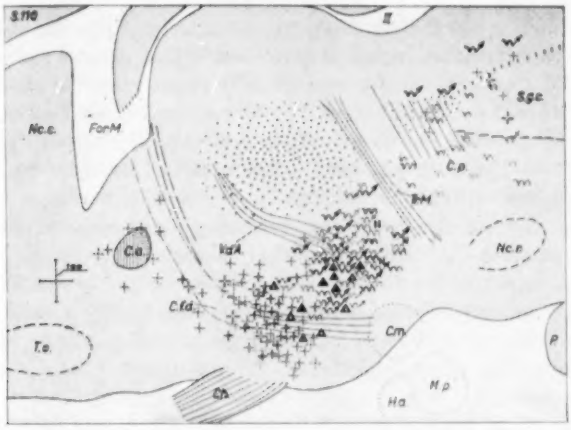

Fig. 4.—Parasagittal section through the diencephalon 2 mm. from the midline, with localization of points yielding sleep and behavioral effects on stimulation.

+ indicates defensive responses; Δ, bulimia; n, increased readiness of response (*Bereitschaft*); m, increased motor activity; n', motor activity passing over to flight. Dotted field = hypnogenous zone. Stippled symbols indicate points stimulated 1 mm. nearer the midline than plotted in Plane 110 (Fig. 1*B*). Dotted symbols indicate points stimulated 1 to 2 mm. lateralward than plotted in Figure 1*B*. Full line = first voltage stage. Light line = second voltage stage.

Note the concentration of points yielding defensive responses in the perifornical zone of the hypothalamus, caudodorsally (in the hypothalamus posterior), and laterally the urge (*Trieb*) to move about and to take flight. The responses last mentioned can be followed back into the central gray matter of the mesencephalon and immediately adjacent structures. The hypnogenous zone (in the middle portion of the ventral nucleus of the thalamus) extends also lateralward beyond Plane 130. The small dotted field should lie 1.5 mm. nearer the midline than indicated, i. e., in the central gray matter dorsal to the opening of the aquaeductus Sylvii.

From Hess, W. R.: Das Zwischenhirn, Basel, Benno Schwabe & Co., 1949.

One of the most conspicuous effects produced by hypothalamic stimulation is certainly the rage reaction, or, as Hess likes to call it, the affective defense reaction. This is an example of complex emotional, autonomic, and somatic behavior produced in a clearly organized way by circumscribed stimulation. The active zone lies in the perifornical hypothalamus, extending slightly backward from here, and forward to

the medial preoptic area and to the base of the septum. Sometimes points situated more posteriorly, as far back as the entrance of the aqueduct, produce the same response (Fig. 4). When stimulated in this region, the cat behaves in a manner similar to that upon seeing a dog. The pupils are dilated; there is piloerection; the animal mews and spits or growls; viscous saliva is secreted; the ears are reflected or move back and forth. Only the curved back is lacking to make the picture complete. If the stimulation is maintained, there is sometimes involuntary micturition and defecation, and finally the animal attacks a person nearby. This can mean only that the effect seen is the expression of an actual emotion, and therefore Hess thinks that the term "sham rage" is inaccurate for describing this reaction. He emphasizes that what is observed here is real rage.

As under normal conditions, the aggressiveness of rage can, when produced by stimulation, change into fear, and the animal will flee away. This rage reaction stops almost immediately when the stimulation is discontinued. The fact that the animal attacks in a well-directed manner is very important. The defense reaction, although elicited not by an external but by an artificially applied internal stimulus, is very well directed against a certain object, in general, the nearest human being. This is the sign of an externally projected internal emotion. The internally created state of emotion identifies an external object as the source of this emotion. That is why the cat finally attacks what it identifies as the object of its rage.

The animal made savage by a transverse cut of the anterior hypothalamus and forebrain, as reported by Bard [4] and others, never attacks in this well-directed manner. The same is true for the even more primitive rage-like reactions obtainable from mesencephalic preparations, as described by Keller.[5] These animals still show the elementary effector mechanism of rage, like growling, piloerection, pupillary dilatation, and striking with extended claws. This proves that there is a lower brain stem mechanism which is able to organize such a behavior, but which is unable to coordinate it in a way adapted to the external situation. In the normal animal this adaptation depends upon sensory information mediated through the cerebral cortex. In the cat visual impressions seem to be the leading ones.

Hess's experiments show that electrical stimulation of a certain hypothalamic area is able to organize sensory, especially visual, impulses into the affective behavioral pattern of rage. Here is an example of a subcortically induced mechanism, which is coordinated with cortical information in order to perform a well-integrated, purposeful act. The rage mechanisms induced by hypothalamic stimulation become projected into the outside world and are blended with an exogenous visual perception.

A completely different behavior, best described as bulimia, is observed when stimulation is carried out slightly posterior to the rage-producing region (Fig. 4). There might be some overlapping of the responses for a distance. After a rather long latency, stimulation induces the animal to search around for food, which, when presented, is eaten with voracity, even when the animal was unwilling to take food before stimulation. Even inedible objects, like a wooden stick, will be bitten and gnawed eagerly. This suggests that stimulation actually induces a state of hunger, perhaps of thirst also. This behavior is accompanied by ergotrope responses, like pupillary dilatation and activation of respiration.

Still more posteriorly another behavior will be induced (Fig. 4). The animal, when stimulated there, becomes restless and a motor behavior appears which sug-

gests an urge to move around without any special goal, and prolonged stimulation very often enhances this motor restlessness until the animal actually escapes. The region producing this effect lies mainly in a parasagittal plane about 2 mm. from the midline in the posterior hypothalamus and subthalamus, extending backward and upward to the pretectum and tectum. From the same points stimulation in anesthetized animals produces rhythmical movements suggestive of walking. This effect tends to fade away when repeated too often or when the stimulus intensity is high, and may then even be replaced after cessation of stimulation by listlessness, drowsiness, and sleep.

LESION EXPERIMENTS

Very small discrete lesions of the hypothalamus are without effect; only bilateral and extensive lesions produce signs. The extent of the lesion seems to matter more than the actual site. The most outstanding features are disturbances in thermoregulation, a stuporous state with loss of the urge to keep clean, cachexia, polycythemia, adiposity, hemorrhagic erosions of the gastric mucosa, and very frequent occurrence of upper respiratory infections, which are always fatal. The regulation of the blood sugar level is disturbed when a lesion is placed in an area of the hypothalamus which roughly covers the region between the descending column of the fornix and the tractus mammillothalamicus. The fact that small lesions fail to produce deficits confirms the lack of precise localization of function in the hypothalamus. Again, the picture arises of a regional representation of certain global performances associating multiple single effects.

CONCLUSIONS

The first consideration shall be the nerve elements which were stimulated in these experiments—cells or fiber tracts, coordinating centers, outflowing paths, or inflowing fiber systems. Actually, we do not know exactly which is the right explanation, and we have to consider all of them. The intermixture of ergotrope and trophotrope responses in the rostral midbrain suggests that there we are stimulating outflowing fiber systems coming from both coordinating centers. On the other hand, the diencephalon must receive information from the periphery, which sets the central integrating mechanisms in action. It is not inconceivable that some of the observed effects depend upon stimulation of such inflowing systems. The highly integrated character of the response, coordinating synergically a group of effectors, might suggest such a possibility. On the other hand, the fact that the rostral midbrain is actually one of the most powerful ergotrope regions might be in favor of the presence of a real coordinating center at this level. The question, therefore, has to be left open, although there seems to be much evidence that in the hypothalamus at least, we are dealing with true coordinative mechanisms.

The second subject to be considered is how these hypothalamic mechanisms are activated in normal life. The ergotrope system is certainly effectively activated by afferent impulses coming from the exteroceptive sense organs. Acoustic impulses, for example, are most effective in arousing a sleeping subject. But others are very effective too, such as light and epicritical pain. This is supported by the anatomical fact that lateral to the posterior commissure the dynamogenous zone is fed by multiple collaterals from the medial lemniscus, to which are joined fibers coming from the tectal area from the lateral and medial geniculate bodies. This provides the possibility for the main pathways destined for the higher cortical centers to

give off collateral impulses which are able to induce subcortically integrated autonomic and motor effects. This mechanism is entirely subcortical in lower animals, for example, in reptiles.

Another activator of the ergotropic system is the cortex, which projects downward into it. One of the main activators seems to be of interoceptive origin. Its role may be primordial. Activation is especially powerful when situations arise where the functional level of circulation and respiration is insufficient to satisfy the required needs for oxidative metabolism. Then a rise in activity is badly needed. The question may be asked whether in this mechanism there may be some centrally effective hormonal component. We do not know, but it seems probable that most of the activation depends on peripheral nerve receptors.

The functions mobilized by the dynamogenous zone create a background upon which the integrated behavior dependent on higher structures may evolve and may be shaped toward its adequate efficiency. It is, therefore, a very important factor in determining the global behavior of the organism.

Considering the physiological activators of trophotrope function, we may say that some of them seem to be located in the walls of hollow organs, like the carotid sinus, the rectum, and the bladder. It is also interesting to note that trophotrope responses may also be activated from quite a different source, namely, the vestibular apparatus. We all know the vagotonic picture of seasickness. It might be of interest to mention here that stimulation in the borderline of the hypnogenous zone induces motor effects resembling position-correcting movements. Hess thinks that there is a representation of vestibular motor mechanisms. As a side-effect, drowsiness occurs, as it often does in motion sickness also. It is, however, not clear what this means from the physiological point of view.

The third consideration is that of the topographical representation of functions within the hypothalamus. After all we know from Hess's work, it would be quite an impossible task to draw an autonomic homunculus for the hypothalamus. The pattern of representation here is obviously different from that of the cerebral cortex. There is no focal representation of specific functions within the hypothalamus. There is collective representation of synergic functions in broad fields, providing a true integration of single functions subserving a specific performance or autonomic needs. Some effects, it is true, have a more focal character, for example, the rage reaction, bulimia, or the motor hyperactivity with tendency to escape. But even so, these focal regions do not correspond to anatomically known nuclear structures but are projected into regions of more reticular structure.

This conception is not invalidated by the fact that in one particular instance of stimulation one particular effect may be more pronounced than others. It also happens in normal life that one function in a particular activity becomes predominant. This is to be understood in terms of some feed-back mechanisms which specifically adjust a particular activity to the functional level required. These adjustments depend upon more peripheral mechanisms. The self-regulation of the single peripheral organ is integrated into more centrally represented functional units, and all of them are again collectively represented and integrated in the hypothalamus.

A last conclusion we might draw from these experiments is that of the relativity of the distinction between what we call autonomic and what we call somatic,

for there is at the diencephalic level no such clear distinction as in the periphery, where the somatic system and the autonomic system are so clearly separated. All complex patterns of nervous activity require the activation of both systems, the best example being perhaps the rage reaction. Here we have a clear somatoautonomic integration; piloerection, for example, and pupillary dilatation are clear autonomic responses, whereas mewing and spitting require the participation of the somatic system. This association of autonomic and somatic, especially subcortical motor, reactions seems to be the main significance of diencephalic physiology. The diencephalon is a place where single actions, autonomic and somatic, are linked together in order to produce a meaningful behavioral pattern. The elementary vegetative functions represented in lower levels of the central nervous system are integrated here into somatic activities dependent upon higher levels in order to produce a purposeful well-integrated effect.

It is very likely that here in the hypothalamus is also the site of the central integration of neural and endocrine mechanisms by means of hypothalamohypophyseal interactions, which may be nervous or humeral or both.

SUMMARY

In summary, then, it can be said that the hypothalamus acts as a nerve structure of highly integrative character. Mainly, it seems to activate and organize global activities of the organism which subserve two main purposes. First, there are the mechanisms subserving the purpose of providing the necessary background for externally directed action and reaction; these are the ergotrope activities, mediated in the periphery mainly by the sympathetic nervous system. The second group of mechanisms subserve the purpose of counteracting exhaustion and overstrain and of maintaining the homeostasis of the organism; these are the trophotrope activities and are mediated in the periphery, mainly by the parasympathetic nervous system. Neither activity is purely autonomic in a strict sense, because there is some degree of somatoautonomic integration in these global performances. Each activity is represented in a different area of the basal diencephalon. The ergotrope area covers roughly the posterior medial hypothalamus and shows a pattern of collective representation of ergotrope activities. The ergotrope or "dynamogenous" zone of the hypothalamus is, therefore, functionally homogeneous. Not so the trophotrope zone, which covers an area comprising the septum, the preoptic area, the lateral hypothalamus, and part of the basal medial thalamus. There some topical organization can be seen, with the exception of the lateral preoptic and anterior lateral hypothalamic area, where a pattern of collective representation of trophotrope mechanism is also encountered.

The main characteristic of the functional organization of the hypothalamus is, therefore, quite different from that of the cortex, where the somatotopic type of representation is dominant. In the hypothalamus another principle of organization is realized; there is collective representation of various organotropic effects into global mechanisms subserving common purposes. This integration of various effectors, autonomic and somatic, into patterns of action, each subserving a definite type of performance, seems to be the main characteristic of the functional organization of the hypothalamus.

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Abstracts from Current Literature

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Psychiatry and Psychopathology

PSYCHOGENIC VOMITING IN CHILDREN. P. C. LAYBOURNE JR., A. M. A. Am. J. Dis. Child. **86**:726 (Dec.) 1953.

Vomiting may be the first indication of an emotional disorder in an infant or child and in some cases is the only obvious symptom. Several mechanisms may be responsible for the vomiting. Repressed hostility may be one reason. Other reasons may be identification with a pregnant mother (in girls), identification with an ill parent, or fantasied ingestion of a love object.

The infant has only a few ways in which to express emotional tension. If the mother can communicate happy feelings to the infant by emphatic means—and it is believed she can—it is reasonable to assume that emotional disturbances in the mother can likewise be so communicated. Many of the so-called feeding problems may be related to severe emotional disturbances in the mother.

Psychological vomiting in children is easily diagnosed by hospitalizing them, for vomiting almost universally stops with removal of the baby from the disturbing home environment. The treatment of these infants requires that the basic emotional difficulty in the parents be resolved.

The child of school age or older is more difficult to treat, and combined therapy of parent and child is often necessary. In these cases the vomiting appears frequently after an operation or other illness. These traumatic experiences are not the "cause" of the vomiting but the trigger mechanism.

The symptom of vomiting is often misinterpreted or overlooked. Later it is appreciated that persistent and recurring vomiting has been present long before obsessions, compulsions, and other forms of behavior problems.

SIEKERT, Rochester, Minn.

THOUGHTS UPON THE EQUATION OF MIND WITH BRAIN. F. M. R. WALSHE, Brain **76**:1 (March) 1953.

In the 13th Hughlings Jackson Lecture, Walshe expresses his reluctance to accept the rather presumptive concepts of some workers who describe the brain and mind as a computing device, which models by its symbols the external world, in terms of a very special and limited type of its own symbolism, that of logic and mathematics. He believes that the concept of soul, and certain religious, ethical, and esthetic values, cannot be "comprehended in terms of action potentials." For him the objective physicomathematical concept of the human mind is evidence of decadence unworthy of the dignity of man. "Man was not made for science, but science by Man, who remains more and greater than his creations."

JOHNS, New York.

Meninges and Blood Vessels

PNEUMOCOCCIC MENINGITIS. J. D. ALEXANDER, H. F. FLIPPIN, and G. M. EISENBERG, A. M. A. Arch. Int. Med. **91**:440 (April) 1953.

The series here reported comprises 102 cases of pneumococcal meningitis seen during the past decade. Autopsy records were available in 68 cases. In analyzing the series, an attempt was made to determine the effect on mortality rates of such factors as (1) age, (2) primary focus of infection, (3) coma, (4) bacteremia, (5) serological type of invading organism, (6) time of institution of therapy in relation to the time of onset of the disease, and (7) type of therapy.

On the basis of the findings in these 102 cases the authors drew the following conclusions:

1. With respect to age, the prognosis for recovery from pneumococcal meningitis is more favorable in the 1- to 15-year-old group than that in other age groups.

2. The mortality rate of the disease does not appear to be influenced significantly by the presence of bacteremia or coma.

3. When the meningitis is secondary to pneumonia, the mortality rate of the disease is significantly higher than that encountered when the sinuses, middle ear, mastoid, or head trauma is involved.

4. Pneumococci of Types 4 and 12 were encountered in a significantly greater number of cases and were associated with a greater number of deaths than other types.

5. Penicillin alone, or penicillin in combination with sulfonamides, is more effective in reducing the mortality rate of the disease than are sulfonamides alone, or the sulfonamides in combination with type-specific anti-Pneumococcus serum. The extent to which penicillin will affect the mortality rate is most probably influenced by the speed with which therapy is begun and by the intensity of the therapy.

The authors feel that rapid roentgenologic investigation of the chest, sinuses, and mastoids, judicious utilization of laboratory facilities and clinical aids, immediate institution of combined penicillin and sulfonamide therapy or massive systemic penicillin therapy, and surgical intervention in cases in which the primary site of the disease can be unequivocally established represent the proper management of this disease.

ALPERS, Philadelphia.

LISTERIA MENINGITIS. M. BINDER, C. DIEHL, J. WEISS, and H. RAY, Ann. Int. Med. **38**:1315 (June) 1953.

Binder and associates describe a case of meningitis due to Listeria monocytogenes. The patient was thought to have tuberculous meningitis, and therapy was begun before recovery of the organism was accomplished. The infection responded to streptomycin and chloramphenicol.

This patient did not present a picture typical of tuberculous meningitis. In addition to his rather alert appearance, the laboratory findings of a leucocytosis, with a count of 24,000 per cubic millimeter, and a spinal fluid sugar of 0, and the rapid subsidence of fever after the onset of therapy were disquieting features of the diagnosis.

The importance of obtaining an adequate number of cultures of spinal fluid before starting therapy in cases of suspected tuberculous meningitis is apparent. But since it is desirable to start streptomycin therapy as early as possible in tuberculous meningitis, it is often necessary to initiate treatment without actual demonstration of tubercle bacilli. Under these circumstances the possibility of Listeria meningitis should be considered. If Listeria organisms can be isolated, the prognosis is probably radically altered and the prolonged therapy for tuberculous meningitis can be avoided.

Streptomycin was administered intramuscularly for seven days; chloramphenicol, for 21 days. The patient's course was that of continued improvement. He was afebrile on his fifth hospital day and remained so. Two months after discharge he reported that he was feeling well except for the occurrence of frequent headaches and backaches.

ALPERS, Philadelphia.

LATE MENINGEAL REACTION TO ETHYL IODOPHENYLUNDECYLATE USED IN MYELOGRAPHY. T. C. ERICKSON and H. J. VAN BAAREN, J. A. M. A. **153**:636 (Oct. 17) 1953.

Severe reactions to the use of ethyl iodophenylundecylate (Pantopaque) as a contrast medium in myelography are uncommon. Usually only transitory and minimal reactions occur. This report concerns a patient who died 15 months after myelography was done with ethyl iodophenylundecylate because of an exudative and adhesive arachnoiditis, producing an obstruction of the fourth ventricle and basal cisternae. That this meningeal reaction was due to ethyl iodophenylundecylate was indicated by x-ray studies, both ante mortem and post mortem, by the chemical determination of iodine in the exudate, and by the microscopic examination.

For two days after myelography the patient had a high temperature and complained of headache and of a flushed face. This immediate reaction, not unusual, was followed by an apparent quiescent period of nine months, during which the symptoms due to the original spinal cord lesion improved. This asymptomatic period may have occurred because the meningeal reaction was a low-grade one, slowly progressive, and caused symptoms only when the exudate became extensive enough to produce obstruction to the free circulation of the cerebrospinal fluid. There followed another six months of progressively severer headaches and other symptoms, which may have been related to the obstructive hydrocephalus which was consequent to arachnoiditis.

Although such a severe reaction to intracranially administered ethyl iodophenylundecylate is very unusual, it would appear that late reactions of milder degree may produce symptoms, the nature of which is overlooked. The authors reemphasize the importance of careful attention to details of technique, such as removal of the ethyl iodophenylundecylate after myelography and special measures to avoid its introduction into the intracranial subarachnoid space.

ALPERS, Philadelphia.

SPONTANEOUS SPINAL SUBARACHNOID HEMORRHAGE. F. ESPY and W. B. SCOVILLE, J. Nerv. & Ment. Dis. **117**:351 (April) 1953.

A 62-year-old man developed headache, stiff neck, and then paraplegia over a three-day period. The spinal fluid contained almost pure blood, but the cisternal fluid was only pink. A block was demonstrated from the third to the fifth thoracic vertebra. A subarachnoid blood clot was surgically removed from this area. There were no abnormal vessels visible about the spinal cord. The patient regained almost complete function in four months and remained well for seven years.

BERLIN, New York.

SOME COMPLICATIONS OF TEMPORAL ARTERITIS. D. KENDALL, Brit. M. J. **2**:418 (Aug. 22) 1953.

Temporal arteritis has a predilection for elderly persons, particularly those with a disposition to arthritis and arteriosclerosis. The course is often benign, though protracted, but in a large percentage of cases severe complications suddenly appear, which cause the patient to seek medical advice. These include unilateral or bilateral blindness, ocular paralysis, vertigo, cutaneous affections along the course of the temporal vessels, or small multiple ulcerative lesions of the nasal and buccal mucous membranes. The visual damage is usually permanent. Relief of discomfort may be obtained by administration of salicylates. The clinical course of nine patients suffering from temporal arteritis is described.

ECHOLS, New Orleans.

PROGNOSIS AND ROLE OF SURGERY IN SPONTANEOUS INTRACRANIAL HAEMORRHAGE. J. M. SMITH, J. M. HOLMES, and R. C. CONNOLLY, Brit. M. J. **2**:1072 (Nov. 14) 1953.

From a comparison of the results of conservative treatment of 100 patients with spontaneous intracranial hemorrhage and the results in 50 patients on whom angiography and operation were performed, Smith and associates concluded that angiographic study of these patients should be undertaken during the first week after the initial hemorrhage so that surgical procedures may be performed in an attempt to prevent recurrent hemorrhage. Their experience indicates that if the patient survives the first 24 hours after the hemorrhage he is most likely to survive during the ensuing week, but as many will die in the second week as in the first 24 hours unless surgical treatment is instituted. Therefore, if intracranial clots are removed or vascular anomalies are treated by proximal ligation or direct surgical attack during this critical first week, these patients can be greatly benefited and the current high mortality can be materially reduced.

ECHOLS, New Orleans.

Diseases of the Brain

BROMIDE INTOXICATION: REPORT OF 36 CASES. J. D. CAMPBELL, South. M. J. **42**:967 (Nov.) 1949.

Campbell reviews 36 cases of bromide poisoning. Symptoms of moderate bromide intoxication (blood bromide of 50 to 150 mg. per 100 cc.) are slowing of cerebration, impaired memory and concentration, nervousness, anorexia, sleep disturbance (insomnia or hypersomnia), dusky-purplish discoloration of the skin, maculopapular or acne-like rash, headache, dizziness, fatigue, and irritability. Severe intoxication (blood bromide of 150 mg. or above) may cause thickness or slurring of speech, personality change, impaired sense of responsibility, rambling of thought, confusion, hallucinations, delusions, disorientation, lethargy, confabulation, combativeness, excitability, and even delirium. Determination of the bromide content of the blood will facilitate the diagnosis. Unsteady gait, hyperactivity or absence of reflexes, tremors, sluggish pupils, poor coordination, and nystagmus are the neurologic signs of bromide poisoning. Sodium chloride is a specific antidote. In mild cases two enteric-coated, 15-grain (0.975 gm.) sodium chloride tablets may be given four times daily. In the moderate and severe cases the patient should be hospitalized. Here, sodium chloride may also be given intravenously. The author uses isotonic sodium chloride solution intravenously, plus sodium chloride tablets orally, or 2.5% sodium chloride, 1,000 cc. per day, intravenously. Most patients, even with severe intoxication, recover within two weeks. The mortality rate is less than 1%. Prescriptions

containing bromides should always carry a "Do not refill" reminder to the druggist. The sale of bromides has been encouraged since the sale of barbiturates has been restricted. The author feels that the sale of bromides should likewise be put under control.

J. A. M. A.

CRANIAL TRAUMA AND "IMMEDIATE" PAPILLARY EDEMA. R. F. MATERA, H. CASTE, and A. MARTINO, Dia méd. **21**:477 (March 28) 1949.

Matera and collaborators reviewed the records of 350 cases of acute craniocerebral trauma which were compiled during 10 years in a hospital department of neurology and neurosurgery. "Immediate" papilledema occurred in 16 cases (4.5%). It was associated in all cases with a blind spot in the visual field and with engorgement of veins. In all the reported cases papilledema was due to post-traumatic intracranial hypertension without hematoma. Immediate papilledema is bilateral, as a rule, and appears between 48 hours and 10 days after the occurrence of cranial trauma. When it is unilateral, it does not cause amaurosis. Unilateral amaurotic "immediate" papilledema appearing in about 24 hours after cranial trauma indicates hemorrhage of the subarachnoid sheath of the optic nerve. "Immediate" papilledema with intracranial hypertension is preceded by an increased tension of the central retinal artery. There is a pathogenetic relation between the post-traumatic pathologic and physicochemical changes in the cerebral tissue and the occurrence of papilledema. The treatment consists of rest, dehydration, and administration of hypertonic sodium chloride solution, provided the pulse, temperature, respiration, arterial pressure, and mental alertness are within normal limits. Decompression operation is indicated when signs of so-called syndrome of compensation do not improve in the course of treatment for intracranial hypertension. Papilledema disappeared within the first month. Two patients had sequels: hypacusia and diminished visual acuity. Cerebral dysrhythmia was demonstrated in the electroencephalographic tracings of four patients, one or two months after a clinical cure had been obtained. These observations suggest the advisability of periodic clinical and electroencephalographic observations as a means of evaluating the progress of the lesion.

J. A. M. A.

Treatment, Neurosurgery

INFLUENCE OF HYPNOSIS ON THE TREMOR OF PARKINSON'S DISEASE. FRANK A. BUELL and J. PARK BIEHL, Dis. Nerv. System **10**:20 (Jan.) 1949.

The authors were led to the investigation of the effect of hypnosis on the tremor of Parkinson's disease by the known fact that the symptom is often lost during sleep. The results in three patients are reported. In two the tremor could be completely abolished, as shown by the electromyogram, while in the third the tremor was improved, though there was no alteration in the muscle tracing. Preliminary electroencephalograms in the waking state were normal in all cases, and no relationship could be discerned between the cortical potential rhythm and the tremor. There were no changes under hypnotic trance, and the records showed no sleep waves. The authors conclude that hypnosis affords only temporary relief from Parkinsonian tremor and that the procedure is too time-consuming for clinical application. The experiments raise speculative queries as to a possible psychological component and as to the existence of cortical suppressor areas which influence the tremor.

BEATON, Tucson, Ariz.

Muscular System

CLINICAL HISTOLOGIC AND ELECTRICAL STUDIES IN MUSCULAR DYSTROPHIES. A. J. ARIEFF and W. R. KIRSCHBAUM, Neurology **3**:35 (Jan.) 1953.

Arieff and Kirschbaum examined seven patients with progressive muscular dystrophy and five patients with myotonic dystrophy clinically and histopathologically.

Familial or hereditary factors were found in two cases of progressive muscular dystrophy and in two cases of myotonic dystrophy. Pseudohypertrophy was seen in four cases of progressive muscular dystrophy and in one unusual case of myotonic dystrophy with myositis. Testicular atrophy, baldness, and cataracts, single or combined, were frequently observed in myotonic

dystrophies and were absent in progressive muscular dystrophy. Progressive muscular atrophy may have progressed to degeneration of the spinal motor neurons in two cases. Spinal cord changes in myotonic dystrophies were not observed.

The histologic criteria for a primary myodegeneration include normal nerve fibers and well-preserved motor end-plates in and about degenerating muscle fibers. This degeneration is limited to portions of the bizarre-shaped, swollen, or shrunken fibers, which soon lead to a disorganized reaction of the muscle nuclei and excessive local amitotic multiplication, with formation of nuclear clusters. Transverse and longitudinal clefts of the muscle fibers appear. The perimysial connective tissue was found to be rather inactive, as was the phagocytic reaction of the reticulo-endothelial system. There was no histolcgic difference between idiopathic and myotonic dystrophy.

Electrical studies were done in 13 cases; 7 were diagnosed as cases of progressive dystrophy, including 1 mixed case with spinal atrophy; 6 were myotonic dystrophy. The results are given in detail. From their findings the authors conclude that myotonic dystrophy has characteristic electrical changes, in contrast to progressive muscular dystrophy.

ALPERS, Philadelphia.

Special Senses

CONGENITAL MYASTHENIA GRAVIS. R. P. WALKER, A. M. A. Am. J. Dis. Child. **86**:198 (Aug.) 1953.

Walker reports the case of an infant girl with congenital myasthenia gravis born of a healthy mother. The past history and the family history were noncontributory, except that the mother was intimately exposed to poliomyelitis early in the pregnancy. The baby was born at full term without difficulty and weighed 8 lb. 2 oz. (3,690 gm.).

She was seen at 2 months of age because of respiratory difficulty and inability to nurse. Since birth the child had been feeble and limp and her cry was weak. She nursed poorly from the breast. At the age of one week milk was noted to run from her nose. She was taken from the breast and given a formula at the age of one month but could take only 1 oz. (30 cc.) at this time. Several weeks later she began having trouble breathing, apparently because of accumulating secretions. Examination revealed a limp, inactive, undernourished infant, with considerable respiratory difficulty. There was slight ptosis of both eyelids; the lips had a bluish tinge. The pharynx contained a large amount of watery secretions. The cry was feeble. There was no anatomic deformity. The gag reflex was hypoactive, and movements of the pharynx and soft palate were slow. The deep tendon reflexes were hypoactive. A therapeutic trial of neostigmine was begun, and within an hour her respiration and ability to expel secretions improved considerably. She became more alert and active, and the ptosis disappeared. The final dose of neostigmine was 5 mg. every four hours. At the age of 8 months she was still taking neostigmine and was getting along fairly well.

SIEKERT, Rochester, Minn.

Encephalography, Ventriculography and Roentgenography

LOCALIZED THINNING AND ENLARGEMENT OF THE CRANIUM WITH SPECIAL REFERENCE TO THE MIDDLE FOSSA. A. E. CHILDE, Am. J. Roentgenol. **70**:1 (July) 1953.

Childe reports 13 cases in which localized thinning and bulging of the cranium caused by an underlying abnormality were demonstrated in skull roentgenograms. In one case the underlying lesion was a subdural hematoma. In seven cases subdural hygromas were found. There was one case of cerebral agenesis or atrophy in which the defect apparently was caused by pressure of an enlarged lateral ventricle against the inner table of the skull. In two cases the defects were caused by slowly growing gliomas. An intracranial aneurysm and neurofibromatosis accounted for the other two cases.

In all 13 cases a localized thinning of the skull was noted in combination with localized enlargement of the cranial cavity. In all but one case a prominence of the outer table of the skull could be detected in the roentgenograms. Often this prominence could be detected clinically. The commonest site of the process is the middle cranial fossa. Elevation of the lesser wing of the sphenoid bone, as seen in posteroanterior skull roentgenograms, is a frequent accompaniment of the bulging and thinning of the cranium. The linea innominata and the lateral wall of the orbit often are obscured in these films. Enlargement of the middle cranial fossa forward and downward

can often be demonstrated in lateral films of the skull, and the forward enlargement can be demonstrated in submentovertex views. Childe draws the conclusion that chronic subdural hygroma is the commonest cause of localized cranial thinning and bulging.

WEILAND, Grove City, Pa.

OCCIPITALIZATION OF THE ATLAS. D. L. MCRAE and A. S. BARNUM, Am. J. Roentgenol. **70**:23 (July) 1953.

McRae and Barnum report 25 cases of occipitalization (assimilation) of the atlas. In making such a diagnosis roentgenographically, one must show some degree of bony union between the skull and the atlas. Lack of movement between the skull and the atlas is not sufficient proof of occipitalization. Platybasia is not necessarily associated with occipitalization of the atlas. Atlanto-occipital joint spaces or atlanto-occipital movement can be demonstrated in nearly all cases of platybasia. Eighteen of the 25 cases showed symptoms which were thought to be referable to a lesion at the foramen magnum and the upper cervical region. Sixteen cases showed positive neurologic signs which were thought to be attributable to the foramen magnum and the upper cervical region. Cases in which symptoms or signs were thought to be explicable on the basis of other neurologic disease were excluded from consideration.

It is not the actual bony fusion of the atlas to the occipital bone which produces symptoms, but it is the soft tissue and bony abnormalities which are often associated with it. The major neurologic symptoms produced are weakness and ataxia of the lower extremities. Numbness and pain in the upper extremities, occipital headache, and blurred vision may be present. Trauma to the head and neck often plays a part in the onset of symptoms. The positive neurologic findings are chiefly long-tract signs in both the upper and the lower extremities. Thus, these lesions produce a syndrome which is very similar to that found in some cases of multiple sclerosis. In over a third of the symptomatic cases in this series a previous misdiagnosis of multiple sclerosis had been made. A search for abnormalities of the cervical spine is indicated in patients with similar complaints and findings before the diagnosis of multiple sclerosis or any other diagnosis is made.

WEILAND, Grove City, Pa.

AGENESIS OF THE CORPUS CALLOSUM. E. F. VAN EPPS, Am. J. Roentgenol. **70**:47 (July) 1953.

Van Epps describes 12 cases of agenesis of the corpus callosum. In four of the cases the malformation was found at autopsy and had not been diagnosed during life. In the other eight the condition was diagnosed during life by pneumoencephalography or ventriculography.

Davidoff and Dyke have described the following roentgenographic characteristics for encephalograms obtained on patients with agenesis of the corpus callosum: (1) abnormally great separation of the lateral ventricles; (2) concave mesial margins and pointed dorsal margins of the lateral ventricles; (3) enlargement of the atria and temporal horns; (4) elongation of interventricular foramens; (5) dorsal extension and dilatation of the third ventricle, and (6) radial arrangement of medial cerebral sulci. Five of the eight patients for whom Van Epps performed an air study showed enlargement of the cisterna magna. Four showed evidence of cortical atrophy. As in other congenital malformations, agenesis of the corpus callosum is often associated with multiple abnormalities of the surrounding neural structures.

WEILAND, Grove City, Pa.

CEREBRAL ANGIOGRAPHY. P. J. HODES, F. CAMPOY, H. E. RIGGS, and P. BLY, Am. J. Roentgenol. **70**:61 (July) 1953.

Hodes and his co-workers injected various portions of the circulatory system in the brains of more than 110 cadavers. After the injections, roentgenograms of the skulls containing the brains were made. Additional roentgenograms of the brain were often made after its removal from the skull, and in some cases roentgenograms of sections of the injected brain were obtained. All the brains were subsequently dissected to compare the findings of the dissections with the roentgenographic findings.

A number of variants of the circle of Willis were demonstrated. The classical form of the circle of Willis, which is usually described in the textbooks of anatomy, was found in 18% of the

cases. The other forms were produced by variations in the sizes of the different arterial branches making up the circle. However, in no case was the circle of Willis incompletely formed. This knowledge is of great practical importance when one must ligate an internal carotid artery, for one can be assured of an adequate circulation in the corresponding side of the brain, which blood supply is obtained from the contralateral internal carotid artery through the circle of Willis. If the circle of Willis were occasionally incomplete, no such assurance would exist and there would be a great hazard in the ligation of an internal carotid artery.

Anomalies of the ascending portion of the anterior cerebral arteries were common. These arteries were often multiple; additional small arteries often arose from the anterior communicating artery, and the anterior cerebral arteries often pursued a slightly tortuous course. When the course of the anterior cerebral artery was tortuous, the path of the artery crossed the midline slightly. However, no appreciable displacement across the midline was ever encountered unless a pathologic lesion was present to account for it.

The origin of the middle cerebral artery as a single branch from the internal carotid artery was not a constant finding. Often two, and even three, middle cerebral vessels branched off the internal carotid artery. However, the pattern of the arterial blood supply to the convexities of the frontal, parietal, temporal, and occipital lobes was fairly constant no matter what the origin of the major middle cerebral arteries. This group of vessels always normally hugged the inner surface of the cranial wall when viewed in the anteroposterior roentgenogram. A widening of the space between these vessels and the inner table of the skull points out the presence of a space-taking lesion, oftenest epidural or subdural hemorrhage. In some brains the cerebral hemispheres were bisected in the sagittal plane, and each portion was studied separately in order to demonstrate the distribution of the anterior and middle cerebral arteries.

The course of the basilar artery was very inconstant. The same could be said of the posterior cerebral arteries, and these arteries even exhibited a complete absence of symmetry in the anteroposterior projection.

The study demonstrated the desirability of obtaining cerebral angiograms routinely as a part of the postmortem study. This is particularly important when the brain is not to be included in the autopsy. In this manner a number of significant cerebral vascular lesions were demonstrated which had not been suspected clinically at the time of death. Hodes discusses the cerebral circulation from the physiologic, as well as the anatomic standpoint, and shows how some of our recent knowledge concerning the physiology of the cerebral circulation is helpful in performing and interpreting cerebral angiograms.

WEILAND, Grove City, Pa.

ROENTGENOLOGIC RECOGNITION OF HABENULAR CALCIFICATION AS DISTINCT FROM CALCIFICATION IN THE PINEAL BODY. H. M. STAUFFER, L. B. SNOW, and A. B. ADAMS, Am. J. Roentgenol. **70**:83 (July) 1953.

Stauffer and his associates have noticed when studying encephalograms that some of the calcification in the region of the pineal body is located anterior to the pineal body proper and is separated from it by the habenular commissure. This calcification is easily located when the third ventricle is filled with air, for it is located in the lateral view between the pineal recess and the suprapineal recess. Oftenest this calcification assumes the shape of the letter C, with the open portion of the C directed posteriorly. When this habenular calcification is present, it is located from 3 to 8 mm. anterior to the center of the pineal calcification. The authors reviewed 285 normal skull roentgenograms and found that 187 of these showed calcification in the region of the pineal body. Forty showed only habenular calcification; 98 showed only pineal calcification, and 49 showed both habenular and pineal calcification. Thus, roughly half of the cases showing calcification in the region of the pineal body show habenular calcification. In determining possible anterior displacement of the pineal body, allowance should be made for the more anterior location of the habenular calcification when this calcification can be identified. Microscopic sections of brains exhibiting habenular calcification show that the calcification is located in the taenia habenulare, and the calcification is separated from the pineal body proper by the habenular commissure.

WEILAND, Grove City, Pa.

ROENTGEN DEMONSTRATION OF THE SEMICIRCULAR CANALS IN PAGET'S DISEASE. K. KETTUNEN, Am. J. Roentgenol. **70**:564 (Oct.) 1953.

In 1950 Newman and Rechtschaffen reported a case of Paget's disease involving the skull in which there was roentgenologic visualization of the semicircular canals. Kettunen adds another case in which roentgenograms of the skull clearly visualize the semicircular canals on both sides in a patient with typical changes of Paget's disease in the skull and in other bones. It is probable that the visualization of the semicircular canals in Paget's disease of the skull is caused by a combination of osteosclerosis of the osseous labyrinths of the inner ears with osteoporosis of the temporal bones. Impairment of function of the inner ear is a characteristic finding in Paget's disease complicated by deafness.

WEILAND, Grove City, Pa.

INTERVERTEBRAL DISC FISSURES (VACUUM INTERVERTEBRAL DISC). J. R. RAINES, Am. J. Roentgenol. **70**:964 (Dec.) 1953.

Raines describes the roentgen appearance produced by the vacuum phenomenon in intervertebral discs. He saw 30 cases over a period of four years in an estimated 3,500 x-ray examinations of the lumbar spine.

The vacuum phenomenon, or phantom nucleus, is a roentgen appearance of radiolucency in the space, or part of the space, normally occupied by the intervertebral disc. When this radiolucency is present, there is usually narrowing of the involved joint space, with marginal sclerosis and production of osteophytes. The vacuum phenomenon is seen oftener when the lumbar spine is extended and usually disappears when the spine is flexed. Post mortem examination has demonstrated cracks in the fibrocartilage of degenerated intervertebral discs, and it is thought that extension of the spine opens the cracks and makes them visible in the roentgenogram.

WEILAND, Grove City, Pa.

Congenital Anomalies

MANDIBULOFACIAL DYSOSTOSIS. P. HURWITZ, A. M. A. Arch. Ophth. **51**:69 (Jan.) 1954.

Mandibulofacial dysostosis is a rare congenital malformation of the facial bones, first described in 1889 by Berry. At that time it also became known as the "Treacher Collins syndrome." There are five forms of the disease: (1) complete; (2) incomplete, in which the deformity is less marked, the ears may be almost normal, but deafness is usually present; (3) abortive, in which only the lid anomalies exist; (4) unilateral, with hypoplasia of the muscles of the face and other symptoms on one side, and (5) atypical.

The palpebral fissures are involved; the malar bones and the mandibles show hypoplasia; malformation of the external ear, and occasionally of the middle and inner ear, is found; high palate and irregular disposition of the teeth, fistulae between the angles of the mouth and the ears, atypical hair growths, facial clefts, and other anatomical deformities occur. Additional features include mental retardation, harelip, clubfoot, and synostosis of the joints. The less salient features are ocular, nasal, oral, aural, and other bony defects of the skull.

The hereditary aspect of the condition has been proved by its appearance in several generations. It seems to have an irregular, dominant form of transmission. The treatment, naturally, depends upon the possibilities of plastic surgery, individual for each case and determined by the deformity.

SPAETH, Philadelphia.

News and Comment

HONORARY MEMBERS, GERMAN SOCIETY FOR NEUROSURGERY

The German Society for Neurosurgery has elected as honorary members Prof. Dr. R. Wartenberg, San Francisco (Honorarprofessor of the University of Freiburg i. Br.), Prof. Dr. L. Schönbauer, Vienna, and Dr. P. Bailey, Chicago.

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The Parents' Trust Is in You

. . . You should know the facts about the Devereux program of *Education with Therapy*

EXCELLENT professional facilities and long experience have equipped Devereux Schools to give effective *education with therapy* to the boy or girl whose emotional disturbances block his normal ability to learn.

Under the guidance of psychiatrists, the staff develops a highly individualized program for each child. The group in which the child lives is chosen carefully to meet his social and educational needs, providing constant companionship and consistent stimulation towards natural family relationships.

You may have occasion to advise parents whose child may benefit from this program. The Devereux Schools staff will be pleased to study the case carefully and offer a detailed report on the possibility of utilizing the Devereux program of education with therapy.

Please address your inquiries to:
John M. Barclay, *Director of Development,* Devon, Pa.

"HUMANI NIHIL A ME ALIENUM PUTO"
THE DEVEREUX FOUNDATION
CALIFORNIA PENNSYLVANIA

Devereux Schools

HELENA T. DEVEREUX, *Director*
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